

BICYCLIC UREA, THIOUREA, GUANIDINE AND CYANOGUANIDINE COMPOUNDS USEFUL FOR THE TREATMENT OF PAIN

BACKGROUND OF THE INVENTION

[0001] The present invention relates to novel compounds, to pharmaceutical compositions comprising the compounds, to processes for making the compounds and to the use of the compounds in therapy. More particularly, it relates to bicyclic urea, thiourea, guanidine and cyanoguanidine compounds which exhibit TrkA kinase inhibition and which are useful in the treatment of pain, cancer, inflammation/inflammatory diseases, neurodegenerative diseases, certain infectious diseases, Sjogren's syndrome, endometriosis, diabetic peripheral neuropathy, prostatitis and pelvic pain syndrome.

[0002] The current treatment regimens for pain conditions utilize several classes of compounds. The opioids (such as morphine) have several drawbacks including emetic, constipatory and negative respiratory effects, as well as the potential for addictions. Non-steroidal anti-inflammatory analgesics (NSAIDs, such as COX-1 or COX-2 types) also have drawbacks including insufficient efficacy in treating severe pain. In addition, COX-1 inhibitors can cause ulcers of the mucosa. Accordingly, there is a continuing need for new and more effective treatments for the relief of pain, especially chronic pain.

[0003] Trk's are the high affinity receptor tyrosine kinases activated by a group of soluble growth factors called neurotrophins (NT). The Trk receptor family has three members: TrkA, TrkB and TrkC. Among the neurotrophins are (i) nerve growth factor (NGF) which activates TrkA, (ii) brain-derived neurotrophic factor (BDNF) and NT-4/5 which activate TrkB and (iii) NT3 which activates TrkC. Trk's are widely expressed in neuronal tissue and are implicated in the maintenance, signaling and survival of neuronal cells (Patapoutian, A. et al., *Current Opinion in Neurobiology*, 2001, 11, 272-280).

[0004] Inhibitors of the Trk/neurotrophin pathway have been demonstrated to be effective in numerous pre-clinical animal models of pain. For example, antagonistic NGF and TrkA antibodies such as RN-624 have been shown to be efficacious in inflammatory and neuropathic pain animal models (Woolf, C.J. et al. (1994) *Neuroscience* 62, 327-331; Zahn, P.K. et al. (2004) *J. Pain* 5, 157-163; McMahon, S.B. et al., (1995) *Nat. Med.* 1, 774-780; Ma, Q. P. and Woolf, C. J. (1997) *NeuroReport* 8, 807-810; Shelton, D. L. et al. (2005) *Pain* 116, 8-16; Delafoy, L. et al. (2003) *Pain* 105, 489-497; Lamb, K. et al. (2003) *Neurogastroenterol. Motil.* 15, 355-361; Jaggar, S. I. et al. (1999) *Br. J. Anaesth.* 83, 442-448) and neuropathic pain animal models (Ramer, M. S. and Bisby, M. A. (1999) *Eur. J. Neurosci.* 11, 837-846; Ro, L. S. et al. (1999); Herzberg, U. et al., *Pain* 79, 265-274 (1997) *Neuroreport* 8, 1613-1618;

Theodosiou, M. et al. (1999) *Pain* 81, 245–255; Li, L. et al. (2003) *Mol. Cell. Neurosci.* 23, 232–250; Gwak, Y. S. et al. (2003) *Neurosci. Lett.* 336, 117–120).

[0005] It has also been shown that NGF secreted by tumor cells and tumor invading macrophages directly stimulates TrkA located on peripheral pain fibers. Using various tumor models in both mice and rats, it was demonstrated that neutralizing NGF with a monoclonal antibody inhibits cancer related pain to a degree similar or superior to the highest tolerated dose of morphine. Because TrkA kinase may serve as a mediator of NGF driven biological responses, inhibitors of TrkA and/or other Trk kinases may provide an effective treatment for chronic pain states.

[0006] Recent literature has also shown that overexpression, activation, amplification and/or mutation of Trk kinases are associated with many cancers including neuroblastoma (Brodeur, G. M., *Nat. Rev. Cancer* 2003, 3, 203-216), ovarian (Davidson, B., et al., *Clin. Cancer Res.* 2003, 9, 2248-2259), colorectal cancer (Bardelli, A., *Science* 2003, 300, 949), melanoma (Truzzi, F., et al., *Dermato-Endocrinology* 2008, 3 (1), pp. 32-36), head and neck cancer (Yilmaz, T., et al., *Cancer Biology and Therapy* 2010, 10 (6), pp. 644-653), gastric carcinoma (Du, J. et al., *World Journal of Gastroenterology* 2003, 9 (7), pp. 1431-1434), lung carcinoma (Ricci A., et al., *American Journal of Respiratory Cell and Molecular Biology* 25 (4), pp. 439-446), breast cancer (Jin, W., et al., *Carcinogenesis* 2010, 31 (11), pp. 1939-1947), Glioblastoma (Wadhwa, S., et al., *Journal of Biosciences* 2003, 28 (2), pp. 181-188), medulloblastoma (Gruber-Olipitz, M., et al., *Journal of Proteome Research* 2008, 7 (5), pp. 1932-1944), secretory breast cancer (Euthus, D.M., et al., *Cancer Cell* 2002, 2 (5), pp. 347-348), salivary gland cancer (Li, Y.-G., et al., *Chinese Journal of Cancer Prevention and Treatment* 2009, 16 (6), pp. 428-430), papillary thyroid carcinoma (Greco, A., et al., *Molecular and Cellular Endocrinology* 2010, 321 (1), pp. 44-49) and adult myeloid leukemia (Eguchi, M., et al., *Blood* 1999, 93 (4), pp. 1355-1363). In preclinical models of cancer, non-selective small molecule inhibitors of TrkA, B and C were efficacious in both inhibiting tumor growth and stopping tumor metastasis (Nakagawara, A. (2001) *Cancer Letters* 169:107-114; Meyer, J. et al. (2007) *Leukemia*, 1–10; Pierottia, M.A. and Greco A., (2006) *Cancer Letters* 232:90–98; Eric Adriaenssens, E., et al. *Cancer Res* (2008) 68:(2) 346-351).

[0007] In addition, inhibition of the neurotrophin/Trk pathway has been shown to be effective in treatment of pre-clinical models of inflammatory diseases with NGF antibodies or non-selective small molecule inhibitors of TrkA. For example, inhibition of the neurotrophin/Trk pathway has been implicated in preclinical models of inflammatory lung diseases including asthma (Freund-Michel, V; Frossard, N., *Pharmacology & Therapeutics* (2008) 117(1), 52-76), interstitial

cystitis (Hu Vivian Y; et. al. *The Journal of Urology* (2005), 173(3), 1016-21), bladder pain syndrome (Liu, H.-T., et al., (2010) *BJU International*, 106 (11), pp. 1681-1685), inflammatory bowel diseases including ulcerative colitis and Crohn's disease (Di Mola, F. F, et. al., *Gut* (2000) 46(5), 670-678) and inflammatory skin diseases such as atopic dermatitis (Dou, Y.-C., et. al. *Archives of Dermatological Research* (2006) 298(1), 31-37), eczema and psoriasis (Raychaudhuri, S. P., et al., *J. Investigative Dermatology* (2004) 122(3), 812-819).

[0008] The TrkA receptor is also thought to be critical to the disease process of the parasitic infection of *Trypanosoma cruzi* (Chagas disease) in human hosts (de Melo-Jorge, M. et al., *Cell Host & Microbe* (2007) 1(4), 251-261).

[0009] Trk inhibitors may also find use in treating disease related to an imbalance of the regulation of bone remodeling, such as osteoporosis, rheumatoid arthritis, and bone metastases. Bone metastases are a frequent complication of cancer, occurring in up to 70 percent of patients with advanced breast or prostate cancer and in approximately 15 to 30 percent of patients with carcinoma of the lung, colon, stomach, bladder, uterus, rectum, thyroid, or kidney. Osteolytic metastases can cause severe pain, pathologic fractures, life-threatening hypercalcemia, spinal cord compression, and other nerve-compression syndromes. For these reasons, bone metastasis is a serious and costly complication of cancer. Therefore, agents that can induce apoptosis of proliferating osteoblasts would be highly advantageous. Expression of TrkA receptors has been observed in the bone-forming area in mouse models of bone fracture (K. Asaumi, et al., *Bone* (2000) 26(6) 625-633). In addition, localization of NGF was observed in almost all bone-forming cells (K. Asaumi, et al.). Recently, it was demonstrated that a Trk inhibitor inhibits the signaling activated by neurotrophins binding to all three of the Trk receptors in human hFOB osteoblasts (J. Pinski, et al., (2002) 62, 986-989). These data support the rationale for the use of Trk inhibitors for the treatment of bone remodeling diseases, such as bone metastases in cancer patients.

[0010] Trk inhibitors may also find use in treating diseases and disorders such as Sjogren's syndrome (Fauchais, A.L., et al., (2009) *Scandinavian Journal of Rheumatology*, 38(1), pp. 50-57), endometriosis (Barcena De Arellano, M.L., et al., (2011) *Reproductive Sciences*, 18(12), pp. 1202-1210; Barcena De Arellano, et al., (2011) *Fertility and Sterility*, 95(3), pp. 1123-1126; Cattaneo, A., (2010) *Current Opinion in Molecular Therapeutics*, 12(1), pp. 94-106), diabetic peripheral neuropathy (Kim, H.C., et al., (2009) *Diabetic Medicine*, 26 (12), pp. 1228-1234; Siniscalco, D., et al., (2011) *Current Neuropharmacology*, 9(4), pp. 523-529; Ossipov, M.H., (2011) *Current Pain and Headache Reports*, 15(3), pp. 185-192), and

prostatitis and pelvic pain syndrome (Watanabe, T., et al., (2011) BJU International, 108(2), pp. 248-251; and Miller, L.J., et al., (2002) Urology, 59(4), pp. 603-608).

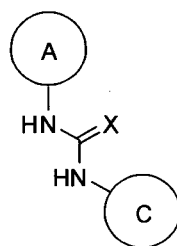
[0011] Several classes of small molecule inhibitors of Trk kinases said to be useful for treating pain or cancer are known (*Expert Opin. Ther. Patents* (2009) 19(3), 305-319).

SUMMARY OF THE INVENTION

[0012] It has now been found that pyrrolidinyl urea, thiourea, guanidine and cyanoguanidine compounds are inhibitors of TrkA, and useful for treating disorders and diseases such as pain, including chronic and acute pain. Compounds of the invention useful in the treatment of multiple types of pain including inflammatory pain, neuropathic pain, and pain associated with cancer, surgery, or bone fracture. In addition, compounds of the invention are useful for treating cancer, inflammation or inflammatory diseases, neurodegenerative diseases, certain infectious diseases, Sjogren's syndrome, endometriosis, diabetic peripheral neuropathy, prostatitis or pelvic pain syndrome, and diseases related to an imbalance of the regulation of bone remodeling, such as osteoporosis, rheumatoid arthritis, and bone metastases.

[0013] Representative compounds of the invention (See Table B below), were found to be highly selective for TrkA over a panel of about 230 other kinases at 10 μ M concentration. In addition, compounds of the invention such as those shown in Table A below, were found to be at least 1000 fold more selective for TrkA versus p38 α .

[0014] More specifically, provided herein are compounds of Formula I:



[0015] or stereoisomers, tautomers, or pharmaceutically acceptable salts, solvates or prodrugs thereof, wherein Ring A, Ring C and X are as defined herein.

[0016] Another aspect of the present invention provides methods of treating a disease or disorder modulated by TrkA, comprising administering to a mammal in need of such treatment an effective amount of a compound of this invention or a stereoisomer, solvate or pharmaceutically acceptable salt thereof. In one embodiment, the disease and disorders include chronic and acute pain, including but not limited to inflammatory pain, neuropathic pain, and pain associated with cancer, surgery, or bone fracture. In another embodiment, the disease and disorders include, but are not limited to, cancer, inflammation or inflammatory diseases,

neurodegenerative diseases, certain infectious diseases, Sjogren's syndrome, endometriosis, diabetic peripheral neuropathy, prostatitis or pelvic pain syndrome, and diseases related to an imbalance of the regulation of bone remodeling, such as osteoporosis, rheumatoid arthritis, and bone metastases. In one embodiment, the treatment includes treating the mammal with a compound of this invention in combination with an additional therapeutic agent.

[0017] Another aspect of the present invention provides a pharmaceutical composition comprising a compound of the present invention or a pharmaceutically acceptable salt thereof.

[0018] Another aspect of the present invention provides the compounds of the present invention for use in therapy.

[0019] Another aspect of the present invention provides the compounds of the present invention for use in the treatment of disease and disorders such as chronic and acute pain, including but not limited to inflammatory pain, neuropathic pain, and pain associated with cancer, surgery, or bone fracture. Another aspect of the present invention provides the compounds of the present invention for use in the treatment of disease and disorders selected from cancer, inflammation or inflammatory diseases, neurodegenerative diseases, certain infectious diseases, Sjogren's syndrome, endometriosis, diabetic peripheral neuropathy, prostatitis or pelvic pain syndrome, and diseases related to an imbalance of the regulation of bone remodeling, such as osteoporosis, rheumatoid arthritis, and bone metastases.

[0020] Another aspect of the present invention provides the use of a compound of this invention in the manufacture of a medicament for the treatment of disease and disorders such as chronic and acute pain including, but not limited to, inflammatory pain, neuropathic pain, and pain associated with cancer, surgery, or bone fracture.

[0021] Another aspect of the present invention provides the use of a compound of this invention in the manufacture of a medicament for the treatment of disease and disorders selected from cancer, inflammation or inflammatory diseases, neurodegenerative diseases, certain infectious diseases, Sjogren's syndrome, endometriosis, diabetic peripheral neuropathy, prostatitis or pelvic pain syndrome, and diseases related to an imbalance of the regulation of bone remodeling, such as osteoporosis, rheumatoid arthritis, and bone metastases.

[0022] Another aspect of the present invention provides intermediates for preparing compounds of Formula I.

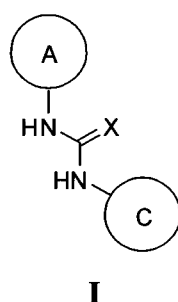
[0023] Another aspect of the present invention includes methods of preparing, methods of separation, and methods of purification of the compounds of this invention.

DETAILED DESCRIPTION OF THE INVENTION

[0024] Provided herein are compounds, and pharmaceutical formulations thereof, that are potentially useful in the treatment of diseases, conditions and/or disorders modulated by TrkA.

[0025] Representative compounds of the invention (See Table B below), were found to be highly selective for TrkA over a panel of about 230 other kinases at 10 μ M concentration. In addition, compounds of the invention such as those shown in Table A below, were found to be at least 1000 fold more selective for TrkA versus p38 α .

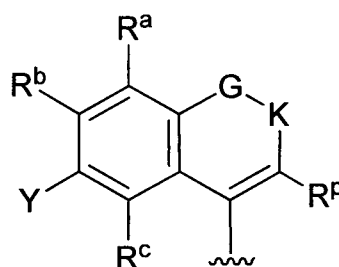
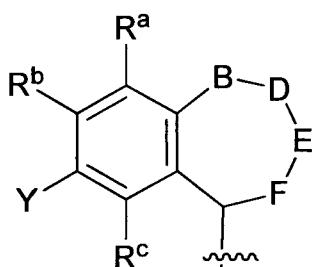
[0026] One embodiment provides a compound of Formula I:



[0027] or stereoisomers, tautomers, or pharmaceutically acceptable salts, solvates or prodrugs thereof, wherein:

[0028] X is O, S, NH or N-CN;

[0029] Ring A is formula A-1 or A-2



[0030] Y is H, halogen, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkyl [optionally substituted with 1-5 fluoros], cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, aminocarbonyl(1-6C)alkyl, (1-6C)alkoxy [optionally substituted with 1-5 fluoros], CN, aminocarbonyl or (1-4C alkoxy)carbonyl;

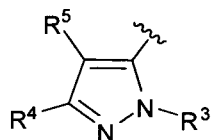
[0031] R^a , R^b and R^c are independently selected from H, halogen, (1-3C)alkyl, (1-3C)alkoxy and CN;

[0032] B is NR^1 , O, a bond, CR^dR^e , S or SO_2 ;

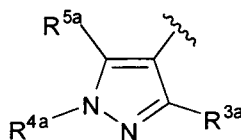
[0033] D is NR^1 , O, a bond, CR^fR^g , S or SO_2 ;

[0034] E is NR^1 , O, a bond, CR^hR^i , S or SO_2 ;

- [0035] F is CR^jR^k ;
- [0036] provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms and zero or one of B, D or E is NR^1 or O;
- [0037] G is CR^mR^n ;
- [0038] K is NR^1 ;
- [0039] R^1 is (1-6C)alkyl [optionally substituted with one to five fluoros], (1-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], (1-6C)alkylC(=O)- or (1-6C alkoxy)C=O-;
- [0040] R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently H, OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], (2-6C)cyanoalkyl, (1-6C)alkoxy [optionally substituted with one to five fluoros], or (1-3C alkoxy)(2-6C)alkoxy [optionally substituted with one to five fluoros],
- [0041] or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring,
- [0042] or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k form an oxo group,
- [0043] and wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom;
- [0044] R^m is H, (1-3C)alkyl [optionally substituted with 1-5 fluoros], cyclopropyl or cyclobutyl, and
- [0045] R^n is H or (1-3C)alkyl [optionally substituted with 1-5 fluoros], or
- [0046] R^m and R^n together form an oxo group;
- [0047] R^p is H, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], or (2-6C)cyanoalkyl;
- [0048] Ring C is formula C-1 or C-2



C-1



C-2

;

[0049] R^3 is (1-6C)alkyl, hydroxy(1-6C)alkyl, Ar^2 , hetCyc¹, (3-7C)cycloalkyl, or hetAr²;

[0050] Ar^2 is phenyl optionally substituted with one or more groups independently selected from halogen and (1-6C)alkyl;

[0051] hetCyc¹ is a 5-6-membered saturated or partially unsaturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

[0052] hetAr² is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

[0053] R^4 is OH, (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, (1-3C)alkylsulfonamido(1-6C)alkyl, sulfamido(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, hetAr³(1-6C)alkyl, Ar^3 (1-6C)alkyl, (1-6C)alkoxy, monofluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, tetrafluoro(2-6C)alkoxy, pentafluoro(2-6C)alkoxy, cyano(1-6C)alkoxy, hydroxy(1-6C)alkoxy, dihydroxy(2-6C)alkoxy, amino(2-6C)alkoxy, hydroxylcarbonyl(1-6C)alkoxy, hetCyc²(1-6C)alkoxy, hetAr³(1-6C)alkoxy, Ar^3 (1-6C)alkoxy, (1-4C alkoxy)(1-6C)alkoxy, (1-3C alkylsulfonyl)(1-6C)alkoxy, (3-6C)cycloalkyl [optionally substituted with F, OH, (1-6C alkyl), (1-6C) alkoxy, or (1-3C alkoxy)(1-6C)alkyl], hetAr⁴, hetAr⁴-O-, Ar^4 , hetCyc²(O)CH₂-, (1-4C alkoxycarbonyl)(1-6C)alkoxy, hydroxycarbonyl(1-6C)alkoxy, aminocarbonyl(1-6C)alkoxy, hetCyc²C(=O)(1-6C)alkoxy, hydroxy(1-3C alkoxy)(1-6C)alkoxy, hydroxytrifluoro(1-6C)alkoxy, (1-3C)alkylsulfonamido(1-6C)alkoxy, (1-3C)alkylamido(1-6C)alkoxy, di(1-3C alkyl)amino-carboxy, hetCyc²C(=O)O-, hydroxydifluoro(1-6C)alkyl, (1-4C alkylcarboxy)(1-6C)alkyl, (1-6C)alkoxycarbonyl, hydroxylcarbonyl, aminocarbonyl, (1-3C alkoxy)aminocarbonyl, hetCyc³, halogen, CN, trifluoromethylsulfonyl, N-(1-3C alkyl)oxadiazolonyl, hetAr⁵ or hetCyc⁴-O-;

[0054] hetCyc² is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with 1-2 groups independently selected from (1-6C)alkyl, (1-4C alkylcarboxy)(1-6C)alkyl, and (1-6C)acyl;

[0055] hetCyc³ is a 4-7 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents

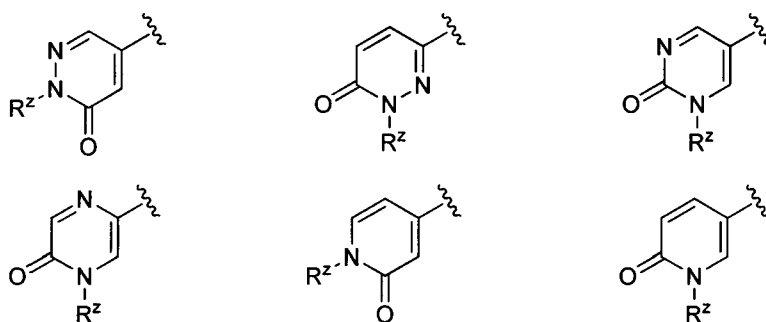
independently selected from F, CN, (1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-6C)acyl-, (1-6C)alkylsulfonyl, trifluoromethylsulfonyl and (1-4C alkoxy)carbonyl;

[0056] hetAr^3 is a 5-membered heteroaryl ring having 1-3 ring atoms independently selected from N, O and S and optionally substituted with (1-6C)alkyl;

[0057] Ar^3 is phenyl optionally substituted with (1-4C)alkoxy;

[0058] hetAr^4 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with one or more substituents independently selected from (1-6C)alkyl, halogen, CN, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, difluoro(1-6C)alkyl, fluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH₂-, (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH₂, (1-6C alkyl)amino, di(1-6C alkyl)amino, (1-3C trifluoroalkoxy), fluoro(1-6C alkyl)amino, difluoro(1-6C alkyl)amino, trifluoro(1-6C alkyl)amino, and (3-4C cycloalkyl)amino;

[0059] hetAr^5 is a group selected from the structures:



[0060] where R^z is (3-4C)cycloalkyl or (1-3C)alkyl (optionally substituted with 1-3 fluoros), wherein each of said hetAr^5 groups is optionally further substituted with one or more groups independently selected from F and (1-3C)alkyl optionally substituted with 1-3 fluoros;

[0061] hetCyc^4 is a 7-8 membered bridged heterocycle having a ring nitrogen atom and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

[0062] Ar^4 is phenyl optionally substituted with one or more groups independently selected from (1-6C)alkyl, halogen, CN, CF₃, CF₃O-, (1-6C)alkoxy, (1-6Calkyl)OC(=O)-, aminocarbonyl, (1-6C)alkylthio, hydroxy(1-6C)alkyl, (1-6C alkyl)SO₂-, HOC(=O)- and (1-3C alkoxy)(1-3C alkyl)OC(=O)-;

[0063] R^5 is (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-3C alkoxy)(1-4C)alkyl, (1-4C alkyl)OC(=O)-, (1-6C)alkylthio, (3-4C)cycloalkyl, amino, aminocarbonyl, trifluoro(1-3C alkyl)amido, or phenyl (optionally

substituted with one or more groups independently selected from halogen, (1-6C)alkyl and (1-6C)alkoxy); or

[0064] R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated, partially unsaturated or unsaturated carbocyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl, or

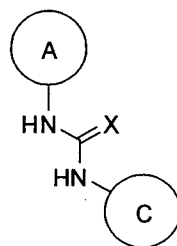
[0065] R^4 and R^5 together with the atoms to which they are attached form 5-6 membered saturated, partially unsaturated or unsaturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or two substituents independently selected from (1-6C alkyl)C(=O)O-, (1-6C)acyl, (1-6C)alkyl and oxo, and said sulfur ring atom is optionally oxidized to S(=O) or SO₂;

[0066] R^{3a} is hydrogen, halogen, (1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (1-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

[0067] R^{4a} is hydrogen, (1-6C)alkyl, trifluoro(1-6C)alkyl, phenyl [optionally substituted with one or more groups independently selected from (1-6C)alkyl, halogen, CN, CF₃, CF₃O-, (1-6C)alkoxy, (1-6Calkyl)OC(=O)-, aminocarbonyl, (1-6C)alkylthio, hydroxy(1-6C)alkyl, (1-6C alkyl)SO₂-, HOC(=O)- and (1-3C alkoxy)(1-3C alkyl)OC(=O)-], or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with 1-2 substituents independently selected from (1-6C)alkyl, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH₂-, (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH₂, (1-6C alkyl)amino, di(1-6C alkyl)amino and (1-3C trifluoroalkoxy)(1-3C)trifluoroalkyl; and

[0068] R^{5a} is hydrogen, halogen, (1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (1-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen.

[0069] In one embodiment compounds of Formula I include Formula I-1:

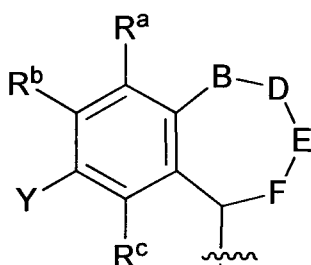


I-1

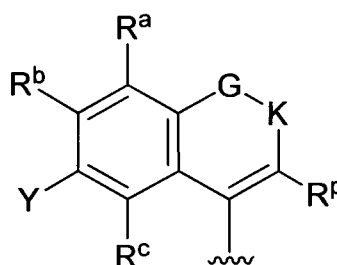
[0070] or stereoisomers, tautomers, or pharmaceutically acceptable salts, or solvates or prodrugs thereof, wherein:

[0071] X is O, S, NH or N-CN;

[0072] Ring A is formula A-1 or A-2



A-1



A-2

[0073] Y is H, halogen, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkyl [optionally substituted with 1-5 fluoros], cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, aminocarbonyl(1-6C)alkyl, (1-6C)alkoxy [optionally substituted with 1-5 fluoros], or CN;

[0074] R^a, R^b and R^c are independently selected from H, halogen, (1-3C)alkyl, (1-3C)alkoxy and CN;

[0075] B is NR¹, O, a bond, or CR^dR^e;

[0076] D is NR¹, O, a bond, or CR^fR^g;

[0077] E is NR¹, O, a bond, or CR^hRⁱ;

[0078] F is CR^jR^k;

[0079] provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms and zero or one of B, D or E is NR¹ or O;

[0080] G is CR^mRⁿ;

[0081] K is NR¹;

[0082] R¹ is (1-6C)alkyl [optionally substituted with one to five fluoros], (1-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], (1-6C)alkylC(=O)- or (1-6C alkoxy)C=O-;

[0083] R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently H, OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], or (2-6C)cyanoalkyl,

[0084] or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring,

[0085] or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k form an oxo group,

[0086] and wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom;

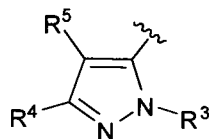
[0087] R^m is H, (1-3C)alkyl [optionally substituted with 1-5 fluoros], cyclopropyl or cyclobutyl, and

[0088] R^n is H or (1-3C)alkyl [optionally substituted with 1-5 fluoros], or

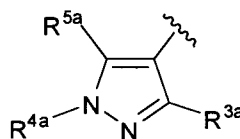
[0089] R^m and R^n together form an oxo group;

[0090] R^p is H, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], or (2-6C)cyanoalkyl;

[0091] Ring C is formula C-1 or C-2



C-1



C-2

;

[0092] R^3 is (1-6C)alkyl, hydroxy(1-6C)alkyl, Ar^2 , hetCyc¹, (3-7C)cycloalkyl, or hetAr²;

[0093] Ar^2 is phenyl optionally substituted with one or more groups independently selected from halogen and (1-6C)alkyl;

[0094] hetCyc¹ is a 5-6-membered saturated or partially unsaturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

[0095] hetAr^2 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

[0096] R^4 is OH, (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, (1-3C alkylsulfonamido(1-6C)alkyl, sulfamido(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, hetAr^3 (1-6C)alkyl, Ar^3 (1-6C)alkyl, (1-6C)alkoxy, monofluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, tetrafluoro(2-6C)alkoxy, pentafluoro(2-6C)alkoxy, cyano(1-6C)alkoxy, hydroxy(1-6C)alkoxy, dihydroxy(2-6C)alkoxy, amino(2-6C)alkoxy, hydroxyl-carbonyl(1-6C)alkoxy, hetCyc^2 (1-6C)alkoxy, hetAr^3 (1-6C)alkoxy, Ar^3 (1-6C)alkoxy, (1-4C alkoxy)(1-6C)alkoxy, (1-3C alkylsulfonyl)(1-6C)alkoxy, (3-6C)cycloalkyl [optionally substituted with F, OH, (1-6C alkyl), (1-6C) alkoxy, or (1-3C alkoxy)(1-6C)alkyl], hetAr^4 , $\text{hetAr}^4\text{-O-}$, Ar^4 , $\text{hetCyc}^2(\text{O})\text{CH}_2\text{-}$, (1-4C alkoxy-carbonyl)(1-6C)alkoxy, hydroxycarbonyl(1-6C)alkoxy, aminocarbonyl(1-6C)alkoxy, $\text{hetCyc}^2\text{C(=O)}$ (1-6C)alkoxy, hydroxy(1-3C alkoxy)(1-6C)alkoxy, hydroxytrifluoro(1-6C)alkoxy, (1-3C)alkylsulfonamido(1-6C)alkoxy, (1-3C)alkylamido(1-6C)alkoxy, di(1-3C alkyl)amino-carboxy, $\text{hetCyc}^2\text{C(=O)}\text{O-}$, hydroxydifluoro(1-6C)alkyl, (1-4C alkylcarboxy)(1-6C)alkyl, (1-6C)alkoxy-carbonyl, hydroxyl-carbonyl, aminocarbonyl, (1-3C alkoxy)aminocarbonyl, hetCyc^3 , halogen, CN, trifluoromethylsulfonyl, N-(1-3C alkyl)oxadiazolonyl, or hetAr^5 ;

[0097] hetCyc^2 is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with 1-2 groups independently selected from (1-6C)alkyl, (1-4C alkylcarboxy)(1-6C)alkyl, and (1-6C)acyl;

[0098] hetCyc^3 is a 4-7 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from F, CN, (1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-6C)acyl-, (1-6C)alkylsulfonyl, trifluoromethylsulfonyl and (1-4C alkoxy)carbonyl;

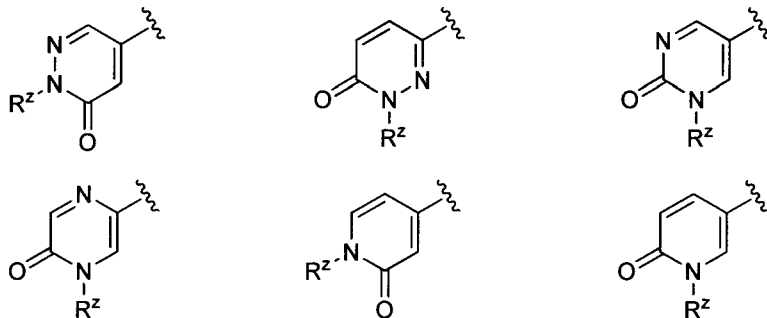
[0099] hetAr^3 is a 5-membered heteroaryl ring having 1-3 ring atoms independently selected from N, O and S and optionally substituted with (1-6C)alkyl;

[00100] Ar^3 is phenyl optionally substituted with (1-4C)alkoxy;

[00101] hetAr^4 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with one or more substituents independently selected from (1-6C)alkyl, halogen, CN, hydroxy(1-6C)alkyl, trifluoro(1-

6C)alkyl, difluoro(1-6C)alkyl, fluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH₂- (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH₂, (1-6C alkyl)amino, di(1-6C alkyl)amino, (1-3C trifluoroalkoxy), fluoro(1-6C alkyl)amino, difluoro(1-6C alkyl)amino, trifluoro(1-6C alkyl)amino, and (3-4C cycloalkyl)amino;

[00102] hetAr⁵ is a group selected from the structures:



[00103] where R^z is (3-4C)cycloalkyl or (1-3C)alkyl (optionally substituted with 1-3 fluoros), wherein each of said hetAr⁵ groups is optionally further substituted with one or more groups independently selected from F and (1-3C)alkyl optionally substituted with 1-3 fluoros;

[00104] Ar⁴ is phenyl optionally substituted with one or more groups independently selected from (1-6C)alkyl, halogen, CN, CF₃, CF₃O-, (1-6C)alkoxy, (1-6Calkyl)OC(=O)-, aminocarbonyl, (1-6C)alkylthio, hydroxy(1-6C)alkyl, (1-6C alkyl)SO₂-, HOC(=O)- and (1-3C alkoxy)(1-3C alkyl)OC(=O)-;

[00105] R⁵ is (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-3C alkoxy)(1-4C)alkyl, (1-4C alkyl)OC(=O)-, (1-6C)alkylthio, (3-4C)cycloalkyl, amino, aminocarbonyl, trifluoro(1-3C alkyl)amido, or phenyl (optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl and (1-6C)alkoxy); or

[00106] R⁴ and R⁵ together with the atoms to which they are attached form a 5-6 membered saturated, partially unsaturated or unsaturated carbocyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl, or

[00107] R⁴ and R⁵ together with the atoms to which they are attached form 5-6 membered saturated, partially unsaturated or unsaturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or two substituents independently selected from (1-6C alkyl)C(=O)O-, (1-6C)acyl, (1-6C)alkyl and oxo, and said sulfur ring atom is optionally oxidized to S(=O) or SO₂;

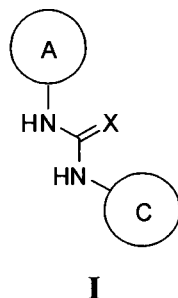
[00108] R^{3a} is hydrogen, halogen, (1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen

and (1-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

[00109] R^{4a} is hydrogen, (1-6C)alkyl, trifluoro(1-6C)alkyl, phenyl [optionally substituted with one or more groups independently selected from (1-6C)alkyl, halogen, CN, CF_3 , CF_3O- , (1-6C)alkoxy, (1-6Calkyl)OC(=O)-, aminocarbonyl, (1-6C)alkylthio, hydroxy(1-6C)alkyl, (1-6C alkyl)SO₂-, HOC(=O)- and (1-3C alkoxy)(1-3C alkyl)OC(=O)-], or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with 1-2 substituents independently selected from (1-6C)alkyl, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH₂- (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH₂, (1-6C alkyl)amino, di(1-6C alkyl)amino and (1-3C trifluoroalkoxy)(1-3C)trifluoroalkyl; and

[00110] R^{5a} is hydrogen, halogen, (1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (1-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen.

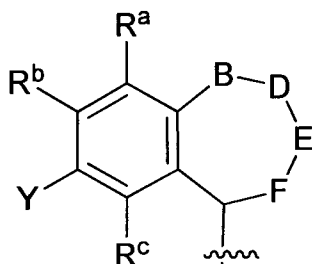
[00111] In one embodiment compounds of Formula I include Formula **I-2**:



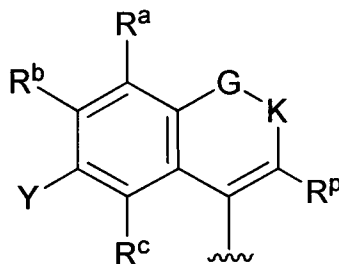
[00112] or stereoisomers, tautomers, or pharmaceutically acceptable salts, solvates or prodrugs thereof, wherein:

[00113] X is O, S, NH or N-CN;

[00114] Ring A is formula A-1 or A-2



A-1



A-2

[00115] Y is H, halogen, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkyl [optionally substituted with 1-5 fluoros], cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, aminocarbonyl(1-6C)alkyl, (1-6C)alkoxy [optionally substituted with 1-5 fluoros], CN, aminocarbonyl or (1-4C alkoxy)carbonyl;

[00116] R^a , R^b and R^c are independently selected from H, halogen, (1-3C)alkyl, (1-3C)alkoxy and CN;

[00117] B is NR^1 , O, a bond, CR^dR^e , S or SO_2 ;

[00118] D is NR^1 , O, a bond, CR^fR^g , S or SO_2 ;

[00119] E is NR^1 , O, a bond, or CR^hR^i , S or SO_2 ;

[00120] F is CR^jR^k ;

[00121] provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms and zero or one of B, D or E is NR^1 or O;

[00122] G is CR^mR^n ;

[00123] K is NR^1 ;

[00124] R^1 is (1-6C)alkyl [optionally substituted with one to five fluoros], (1-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], (1-6C)alkylC(=O)- or (1-6C alkoxy)C=O-;

[00125] R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently H, OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], (2-6C)cyanoalkyl, (1-6C)alkoxy [optionally substituted with one to five fluoros], or (1-3C alkoxy)(2-6C)alkoxy [optionally substituted with one to five fluoros],

[00126] or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring,

[00127] or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k form an oxo group,

[00128] and wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom;

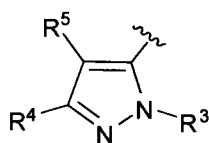
[00129] R^m is H, (1-3C)alkyl [optionally substituted with 1-5 fluoros], cyclopropyl or cyclobutyl, and

[00130] R^n is H or (1-3C)alkyl [optionally substituted with 1-5 fluoros], or

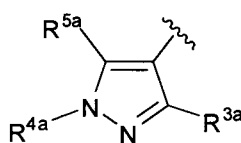
[00131] R^m and R^n together form an oxo group;

[00132] R^p is H, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], or (2-6C)cycloalkyl;

[00133] Ring C is formula C-1 or C-2



C-1



C-2

;

[00134] R^3 is (1-6C)alkyl, hydroxy(1-6C)alkyl, Ar^2 , hetCyc¹, (3-7C)cycloalkyl, or hetAr²;

[00135] Ar^2 is phenyl optionally substituted with one or more groups independently selected from halogen and (1-6C)alkyl;

[00136] hetCyc¹ is a 5-6-membered saturated or partially unsaturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

[00137] hetAr² is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

[00138] R^4 is OH, (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, (1-3C)alkylsulfonamido(1-6C)alkyl, sulfamido(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, hetAr³(1-6C)alkyl, Ar^3 (1-6C)alkyl, (1-6C)alkoxy, monofluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, tetrafluoro(2-6C)alkoxy, pentafluoro(2-6C)alkoxy, cyano(1-

6C)alkoxy, hydroxy(1-6C)alkoxy, dihydroxy(2-6C)alkoxy, amino(2-6C)alkoxy, hydroxyl-carbonyl(1-6C)alkoxy, hetCyc²(1-6C)alkoxy, hetAr³(1-6C)alkoxy, Ar³(1-6C)alkoxy, (1-4C alkoxy)(1-6C)alkoxy, (1-3C alkylsulfonyl)(1-6C)alkoxy, (3-6C)cycloalkyl [optionally substituted with F, OH, (1-6C alkyl), (1-6C) alkoxy, or (1-3C alkoxy)(1-6C)alkyl], hetAr⁴, hetAr⁴-O-, Ar⁴, hetCyc²(O)CH₂-, (1-4C alkoxy carbonyl)(1-6C)alkoxy, hydroxycarbonyl(1-6C)alkoxy, aminocarbonyl(1-6C)alkoxy, hetCyc²C(=O)(1-6C)alkoxy, hydroxy(1-3C alkoxy)(1-6C)alkoxy, hydroxytrifluoro(1-6C)alkoxy, (1-3C)alkylsulfonamido(1-6C)alkoxy, (1-3C)alkylamido(1-6C)alkoxy, di(1-3C alkyl)amino-carboxy, hetCyc²C(=O)O-, hydroxydifluoro(1-6C)alkyl, (1-4C alkylcarboxy)(1-6C)alkyl, (1-6C)alkoxy carbonyl, hydroxylcarbonyl, aminocarbonyl, (1-3C alkoxy)aminocarbonyl, hetCyc³, halogen, CN, trifluoromethylsulfonyl, N-(1-3C alkyl)oxadiazolonyl, hetAr⁵ or hetCyc⁴-O-;

[00139] hetCyc² is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with 1-2 groups independently selected from (1-6C)alkyl, (1-4C alkylcarboxy)(1-6C)alkyl, and (1-6C)acyl;

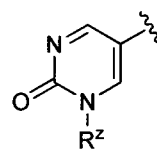
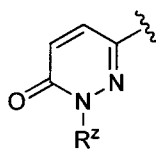
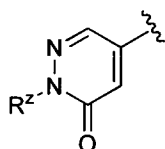
[00140] hetCyc³ is a 4-7 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from F, CN, (1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-6C)acyl-, (1-6C)alkylsulfonyl, trifluoromethylsulfonyl and (1-4C alkoxy)carbonyl;

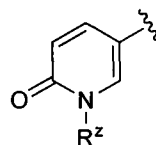
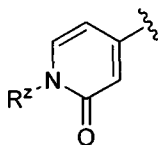
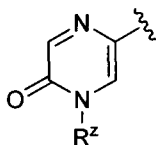
[00141] hetAr³ is a 5-membered heteroaryl ring having 1-3 ring atoms independently selected from N, O and S and optionally substituted with (1-6C)alkyl;

[00142] Ar³ is phenyl optionally substituted with (1-4C)alkoxy;

[00143] hetAr⁴ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with one or more substituents independently selected from (1-6C)alkyl, halogen, CN, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, difluoro(1-6C)alkyl, fluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH₂-, (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH₂, (1-6C alkyl)amino, di(1-6C alkyl)amino, (1-3C trifluoroalkoxy), fluoro(1-6C alkyl)amino, difluoro(1-6C alkyl)amino, trifluoro(1-6C alkyl)amino, and (3-4C cycloalkyl)amino;

[00144] hetAr⁵ is a group selected from the structures:





[00145] where R^Z is (3-4C)cycloalkyl or (1-3C)alkyl (optionally substituted with 1-3 fluoros), wherein each of said hetAr^5 groups is optionally further substituted with one or more groups independently selected from F and (1-3C)alkyl optionally substituted with 1-3 fluoros;

[00146] hetCyc^4 is a 7-8 membered bridged heterocycle having a ring nitrogen atom and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

[00147] Ar^4 is phenyl optionally substituted with one or more groups independently selected from (1-6C)alkyl, halogen, CN, CF_3 , $\text{CF}_3\text{O}-$, (1-6C)alkoxy, (1-6Calkyl)OC(=O)-, aminocarbonyl, (1-6C)alkylthio, hydroxy(1-6C)alkyl, (1-6C alkyl) SO_2- , $\text{HOC}(=\text{O})-$ and (1-3C alkoxy)(1-3C alkyl)OC(=O)-;

[00148] R^5 is (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-3C alkoxy)(1-4C)alkyl, (1-4C alkyl)OC(=O)-, (1-6C)alkylthio, (3-4C)cycloalkyl, amino, aminocarbonyl, trifluoro(1-3C alkyl)amido, or phenyl (optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl and (1-6C)alkoxy); or

[00149] R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated, partially unsaturated or unsaturated carbocyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl, or

[00150] R^4 and R^5 together with the atoms to which they are attached form 5-6 membered saturated, partially unsaturated or unsaturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or two substituents independently selected from (1-6C alkyl)C(=O)O-, (1-6C)acyl, (1-6C)alkyl and oxo, and said sulfur ring atom is optionally oxidized to $\text{S}(=\text{O})$ or SO_2 ;

[00151] R^{3a} is halogen, (1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (1-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

[00152] R^{4a} is hydrogen, (1-6C)alkyl, trifluoro(1-6C)alkyl, phenyl [optionally substituted with one or more groups independently selected from (1-6C)alkyl, halogen, CN, CF_3 , $\text{CF}_3\text{O}-$, (1-

6C)alkoxy, (1-6Calkyl)OC(=O)-, aminocarbonyl, (1-6C)alkylthio, hydroxy(1-6C)alkyl, (1-6C alkyl)SO₂-, HOC(=O)- and (1-3C alkoxy)(1-3C alkyl)OC(=O)-], or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with 1-2 substituents independently selected from (1-6C)alkyl, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH₂-, (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH₂, (1-6C alkyl)amino, di(1-6C alkyl)amino and (1-3C trifluoroalkoxy)(1-3C)trifluoroalkyl; and

[00153] R^{5a} is halogen, (1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (1-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen.

[00154] It is to be understood that in instances where two or more radicals are used in succession to define a substituent attached to a structure, the first named radical is considered to be terminal and the last named radical is considered to be attached to the structure in question. Thus, for example, the radical "alkoxyalkyl" is attached to the structure in question by the alkyl group.

[00155] The terms "(1-6C)alkyl", "(1-4C)alkyl" and "(1-3C)alkyl" as used herein refer to saturated linear monovalent hydrocarbon radicals of one to six carbon atoms, one to four carbon atoms, and one to three carbon atoms, respectively, or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, three to four carbon atoms, or three carbon atoms, respectively. Examples include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-methyl-1-propyl, 2-butyl, 2-methyl-2-propyl, 2,2-dimethylpropyl, 1-pentyl, 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl, and 3,3-dimethyl-2-butyl.

[00156] "(1-4C)Alkoxy", "(1-3C)alkoxy", "(1-6C)alkoxy" and "(2-6C)alkoxy" refer to an -OR radical where R is (1-4C)alkyl, (1-3C)alkyl, (1-6C)alkyl, or (2-6C)alkyl, respectively, as defined above. Examples include methoxy, ethoxy, and the like.

[00157] "(1-6)Acyl" means a RC(=O)- radical where R is a linear saturated monovalent hydrocarbon radical of one to five carbon atoms or a branched saturated monovalent hydrocarbon radical of three to five carbon atoms, e.g., methylcarbonyl, and the like.

[00158] "(1-3C Alkoxy)(1-6C)alkyl" and "(1-3C alkoxy)(1-4C)alkyl" mean a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or one to four carbon

atoms, or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms or three to four carbon atoms, respectively, wherein one of the carbon atoms is substituted with one (1-3C)alkoxy group as defined herein.

[00159] "(1-3C Alkoxy)(1-6C)alkoxy" means a (1-6C)alkoxy group as defined herein, wherein one of the carbon atoms is substituted with a (1-3C)alkoxy group as defined herein. Examples include methoxymethoxy, methoxyethoxy, and the like.

[00160] "(1-3C Alkoxy)aminocarbonyl" means a (1-3C alkyl)-O-NH-C(=O)- group.

[00161] "(1-6C)Alkoxy carbonyl" and "(1-4C)alkoxy carbonyl" mean a (1-6C)-O-C(=O)- and (1-4C)-O-C(=O)- group, respectively.

[00162] "(1-4C Alkoxy carbonyl)(1-6C alkoxy)" means a (1-6C) alkoxy group as defined herein wherein one of the carbon atoms is substituted with one (1-4C alkoxy)carbonyl group, i.e., an alkyl-O-C(=O)- group.

[00163] "(1-3C Alkoxy)hydroxycarbonylalkyl" means a hydroxycarbonylalkyl group as defined herein wherein one of the carbon atoms is substituted with one (1-3C alkoxy) group.

[00164] "Amino" means a -NRR' group where R and R' are independently selected from hydrogen or (1-3C)alkyl as defined herein. Examples include H₂N-, CH₃NH-, (CH₃)₂N-, and the like. "Amino(1-6C)alkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, wherein one of the carbon atoms is substituted with one -NRR' group where R and R' are independently selected from hydrogen or (1-3C)alkyl as defined herein. Examples include aminomethyl, methylaminoethyl, 2-ethylamino-2-methylethyl, and the like.

[00165] "Amino(2-6C)alkoxy" means a (2-6C)alkoxy group as defined herein, wherein one of the carbon atoms is substituted with one -NRR' group where R and R' are independently selected from hydrogen or (1-3C)alkyl as defined herein.

[00166] "Aminocarbonyl" means a RR'NCO- radical where R and R' are independently hydrogen or (1-6C)alkyl as defined herein. Examples include H₂NCO-, dimethylaminocarbonyl, and the like.

[00167] "Aminocarbonyl(1-6C)alkyl" means a linear saturated hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbons wherein one of the carbon atoms is substituted with one aminocarbonyl group as defined herein, e.g., 2-aminocarbonylethyl, 1-, 2-, or 3-dimethylaminocarbonylpropyl, and the like.

[00168] "Aminocarbonyl(1-6C)alkoxy" means a (1-6C)alkoxy as defined herein, wherein one of the carbon atoms is substituted with one aminocarbonyl group as defined herein.

[00169] "(1-3C)Alkylamido(1-6C)alkoxy" means a (1-6C)alkoxy as defined herein, wherein one of the carbon atoms is substituted with one alkylamido group, i.e., substituted with a (1-3C)C(=O)NH- group.

[00170] "(1-4C alkyl)carboxy" means a R'-C(=O)O- group where R' is (1-4C)alkyl.

[00171] "(1-4C alkylsiloxy)(1-6C)alkoxy" means a (1-6C)alkoxy group as defined herein wherein one of the carbon atoms is substituted with one (1-4C alkyl)siloxy group, e.g., a (1-4C alkyl)Si-O- group such as a tert-butyloxy group.

[00172] "(1-3C)Alkylsulfonamido" means a (1-3C)alkylSO₂NH- radical where (1-3C)alkyl is as defined herein.

[00173] "(1-3C Alkylsulfonamido)(1-6C)alkyl" means a linear saturated hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbons substituted with one (1-3C)alkylsulfonamido group as defined herein.

[00174] "(1-3C)Alkylsulfonamido(1-6C)alkoxy" means a (1-6C)alkoxy group as defined herein wherein one of the carbon atoms is substituted with one (1-3C)alkylsulfonamido group as defined herein.

[00175] "Hydroxycarbonyl" means HOC(=O)-.

[00176] "(1-4C alkyl)carboxy(1-6C)alkyl" means a (1-6C)alkyl group as defined herein wherein one of the carbon atoms is substituted with a (1-4C alkyl)carboxy group as defined herein.

[00177] "Cyano(1-6C)alkyl" means a linear saturated hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbons substituted with a cyano (CN) group.

[00178] "(3-6C)Cycloalkyl" means a cyclic saturated monovalent hydrocarbon radical of three to six carbon atoms, e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[00179] "Dihydroxy(2-6C)alkyl" means a linear saturated hydrocarbon radical of two to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbons substituted with two hydroxy (OH) groups, provided that two hydroxy groups are not both on the same carbon atom.

[00180] "Dihydroxy(2-6C)alkoxy" means a (2-6C)alkoxy group as defined herein, wherein two of the carbon atoms are substituted with a hydroxy group.

[00181] "Halogen" as used herein means F, Cl, Br or I.

[00182] "Heterocycle" refers to a saturated or partially unsaturated ring system having one or more ring heteroatoms as recited for the specific heterocyclic group, wherein the

heterocycle is optionally substituted with substituents as defined for that particular heterocyclic group.

[00183] "Heteroaryl" refers to a 5-6 membered unsaturated ringsystem having one or more ring heteroatoms as recited for the specific heteroaryl group, wherein the heteroaryl is optionally substituted with substituents as defined for that particular heteroaryl group.

[00184] "hetCyc²C(=O)(1-6C)alkoxy" means a (1-6C)alkoxy as defined herein, wherein one of the carbon atoms is substituted with a hetCyc²C(=O) group, wherein hetCyc² is as defined herein.

[00185] "Hydroxy(1-6C)alkyl" and "hydroxy(1-4C)alkyl" means a linear saturated hydrocarbon radical of one to six carbon atoms or one to four carbon atoms, respectively, or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms or three to four carbon atoms, respectively, wherein one of the carbon atoms is substituted with a hydroxy (OH) group.

[00186] "Hydroxy(1-6C)alkoxy" means a (1-6C)alkoxy group as defined herein, wherein one of the carbon atoms is substituted with a hydroxy group.

[00187] "Hydroxy(1-3C alkoxy)(1-6C)alkoxy" means a (1-3C alkoxy)(1-6C)alkoxy as defined herein, wherein one of the carbon atoms is substituted with a hydroxy group.

[00188] "Hydroxydifluoro(1-6C)alkyl" means a difluoro(1-6C)alkyl group as defined herein, wherein one of the carbon atoms is substituted with a hydroxy group.

[00189] "Hydroxytrifluoro(1-6C)alkoxy" means a trifluoro(1-6C)alkoxy group as defined herein, wherein one of the carbon atoms is substituted with a hydroxy group.

[00190] "Hydroxycarbonylalkyl" means a linear saturated hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbons substituted with one -COOH group. Examples include 2-hydroxycarbonyl ethyl, 1-, 2-, or 3-hydroxycarbonylpropyl, and the like.

[00191] "Isoindoline-1,3-dionyl(1-6C)alkoxy" means a (1-6C)alkoxy group as defined herein, wherein one of the carbon atoms is substituted with an isoindoline-1,3-dionyl group.

[00192] "Monofluoro(1-6C)alkyl", "difluoro(1-6C)alkyl" and "trifluoro(1-6C)alkyl" refer to a (1-6C)alkyl group as defined herein wherein one to three hydrogen atoms, respectively, is replaced by a fluoro group.

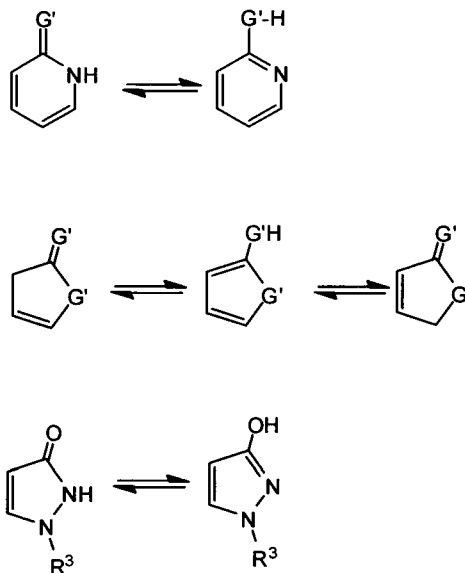
[00193] "Tetrafluoro(2-6C)alkyl" and "pentafluoro(2-6C)alkyl" refer to a linear saturated monovalent hydrocarbon radical of two to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms wherein four to five hydrogen atoms, respectively, is replaced by a fluoro group.

[00194] "Trifluoro(1-3C alkyl)amido" means a (1-3C alkyl)C(=O)NH- group wherein one of the carbons is substituted with three fluoros.

[00195] "Trifluoro(1-6C)alkoxy" means a (1-6C)alkoxy group as defined herein, wherein one of the carbon atoms is substituted with three fluoros.

[00196] "Sulfamido(1-6C)alkyl" means a linear saturated hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbons substituted with one sulfamido (H₂NSO₂NH-) group.

[00197] It should be noted that compounds of the invention may contain groups that may exist in tautomeric forms, such as heteroatom substituted heteroaryl or heterocyclic groups and the like, which are illustrated in the following general and specific examples:



[00198] where G' = O, S, or NR, and though one form is named, described, displayed and/or claimed herein, all the tautomeric forms are intended to be inherently included in such name, description, display and/or claim.

[00199] In one embodiment of Formula I, X is O.

[00200] In one embodiment of Formula I, X is S.

[00201] In one embodiment of Formula I, X is NH.

[00202] In one embodiment of Formula I, X is N-CN.

[00203] In one embodiment of Formula I, Y is H.

[00204] In one embodiment of Formula I, Y is halogen. In one embodiment, Y is F, Cl or Br.

[00205] In one embodiment of Formula I, Y is (1-3C alkoxy)(1-6C)alkyl. In one embodiment, Y is CH₃OCH₂-.

- [00206] In one embodiment of Formula I, Y is (1-6C)alkyl optionally substituted with 1-5 fluoros. In one embodiment, Y is methyl, ethyl, propyl, isopropyl or trifluoromethyl.
- [00207] In one embodiment of Formula I, Y is cyano(1-6C)alkyl. In one embodiment, Y is CNCH₂-.
- [00208] In one embodiment of Formula I, Y is hydroxy(1-6C)alkyl. In one embodiment, Y is HOCH₂.
- [00209] In one embodiment of Formula I, Y is dihydroxy(2-6C)alkyl. In one embodiment, Y is HOCH₂CH(OH).
- [00210] In one embodiment of Formula I, Y is aminocarbonyl(1-6C)alkyl. In one embodiment, Y is H₂NC(=O)CH₂CH₂-, CH₃NHC(=O)CH₂CH₂-, or (CH₃)₂NC(=O)CH₂CH₂-.
- [00211] In one embodiment of Formula I, Y is (1-6C)alkoxy optionally substituted with 1-5 fluoros. In one embodiment, Y is CH₃O-, CH₃CH₂O-, CF₃O- or CF₃CH₂O-.
- [00212] In one embodiment of Formula I, Y is CN.
- [00213] In one embodiment of Formula I, Y is aminocarbonyl. In one embodiment, Y is H₂NC(=O)-.
- [00214] In one embodiment of Formula I, Y is (1-4C alkoxy)carbonyl. In one embodiment, Y is CH₃OC(=O)-.
- [00215] In one embodiment of Formula I, Y is H, halogen or (1-3C alkoxy)(1-6C)alkyl.
- [00216] In one embodiment of Formula I, R^a, R^b and R^c are hydrogen.
- [00217] In one embodiment of Formula I, R^a, R^b and R^c are independently selected from halogen, (1-3C)alkyl, (1-3C)alkoxy and CN.
- [00218] In one embodiment of Formula I, one of R^a, R^b and R^c is selected from halogen, (1-3C)alkyl, (1-3C)alkoxy and CN and the other two are hydrogen.
- [00219] In one embodiment of Formula I, one of R^a, R^b and R^c is selected from halogen and (1-3C)alkoxy and the other two are hydrogen.
- [00220] In one embodiment of Formula I, zero to four of R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j and R^k are independently H, OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], (2-6C)cyanoalkyl, (1-6C)alkoxy [optionally substituted with one to five fluoros], or (1-3C alkoxy)(2-6C)alkoxy [optionally substituted with one to five fluoros], or one of a pair of R^d and R^e, or R^f and R^g, or R^h and Rⁱ, or R^j and R^k, together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring, or one of a pair of R^d and R^e, or R^f and R^g, or R^h and Rⁱ, or R^j and R^k form an oxo group, and the remainder are

hydrogen, wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom.

[00221] In one embodiment of Formula I, zero to four of R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], (1-6C)alkoxy [optionally substituted with one to five fluoros], or (1-3C alkoxy)(2-6C)alkoxy [optionally substituted with one to five fluoros], or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring, or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k form an oxo group, and the remainder are hydrogen, wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom.

[00222] In one embodiment of Formula I, zero to four of R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently OH, methyl, methoxy, cyclopropyl, or 2-methoxyethoxy, or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring, or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k form an oxo group, and the remainder are hydrogen, wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom.

[00223] In one embodiment of Formula I, zero to two of R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], (2-6C)cyanoalkyl, (1-6C)alkoxy [optionally substituted with one to five fluoros], or (1-3C alkoxy)(2-6C)alkoxy [optionally substituted with one to five fluoros], or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to

which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring, or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k form an oxo group, and the remainder are hydrogen, wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom.

[00224] In one embodiment of Formula I, zero to two of R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], (1-6C)alkoxy [optionally substituted with one to five fluoros], or (1-3C alkoxy)(2-6C)alkoxy [optionally substituted with one to five fluoros], or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring, or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k form an oxo group, and the remainder are hydrogen, wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom.

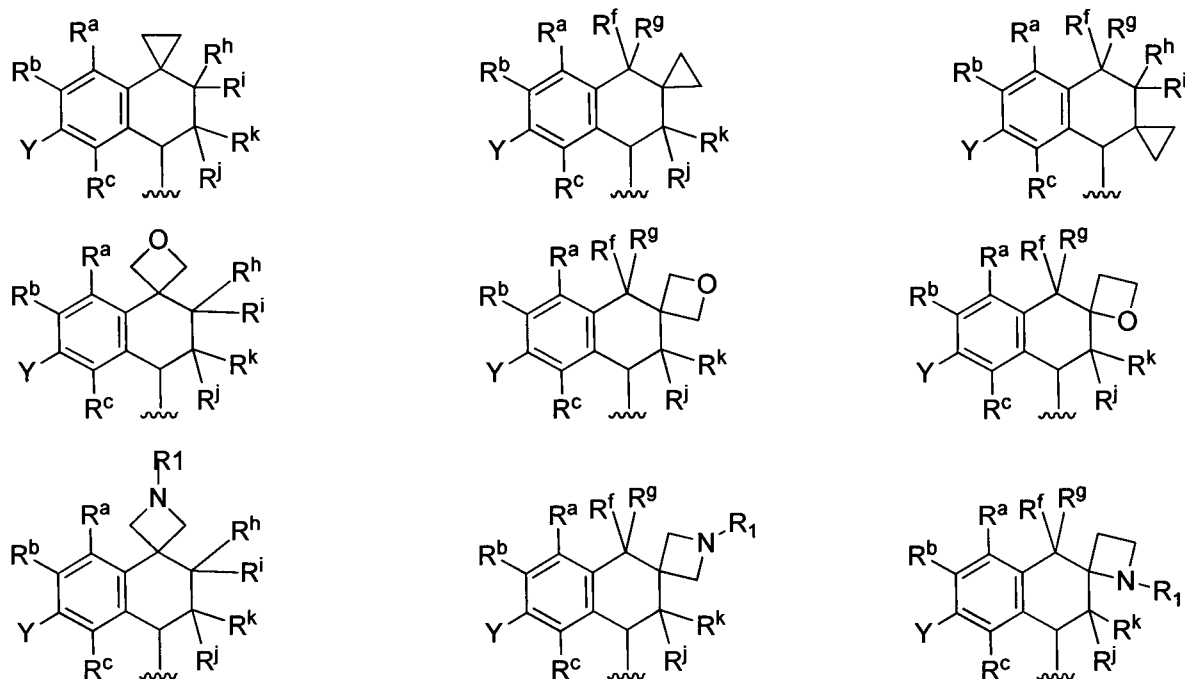
[00225] In one embodiment of Formula I, zero to two of R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently OH, methyl, methoxy, cyclopropyl, or 2-methoxyethoxy, or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring, or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k form an oxo group, and the remainder are hydrogen, wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom.

[00226] In one embodiment of Formula I, one of R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k is halogen or (1-3C)alkoxy, and the remainder are hydrogen.

[00227] In one embodiment of Formula I, R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are hydrogen.

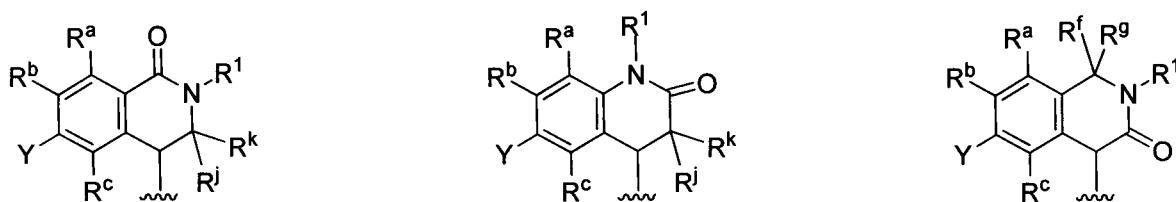
[00228] As used herein, the phrase "one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to which they are attached form a (3-6C)cycloalkyl,

oxetanyl or azetidiny ring" refers a spirocyclic (3-6C)cycloalkyl, oxetanyl or azetidiny ring formed from a pair of said R groups, wherein each R group of said pair is attached to the same carbon atom. Examples of such structures include, but are not limited to the following:



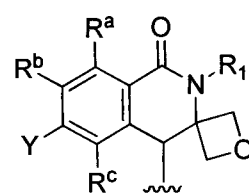
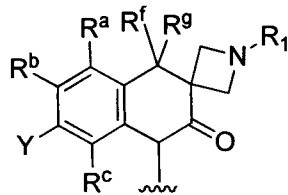
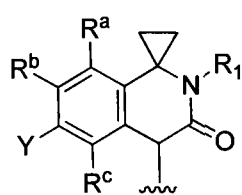
[00229] and the like, wherein the remaining R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently H, OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], or (2-6C)cyanoalkyl and R^1 is H, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], or (2-6C)cyanoalkyl.

[00230] As used herein, the phrase "one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to which they are attached form an oxo group" refers to an oxo group formed from a pair of said R groups, wherein each R group of said pair is attached to the same carbon atom. Examples of such structures include, but are not limited to the following:



[00231] and the like, wherein the remaining R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently H, OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], or (2-6C)cyanoalkyl and R^1 is H, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], or (2-6C)cyanoalkyl.

[00232] The phrase " R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently H, OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], or (2-6C)cyanoalkyl, or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring, or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k form an oxo group" refers to a compound having a spirocyclic group which is formed from a first pair of said R groups, wherein each R group of said first pair is attached to a first carbon atom, and further contains an oxo group formed from a second pair of said R groups, wherein each R group of said second pair is attached to a second carbon atom. Examples of such structures include, but are not limited to the following:

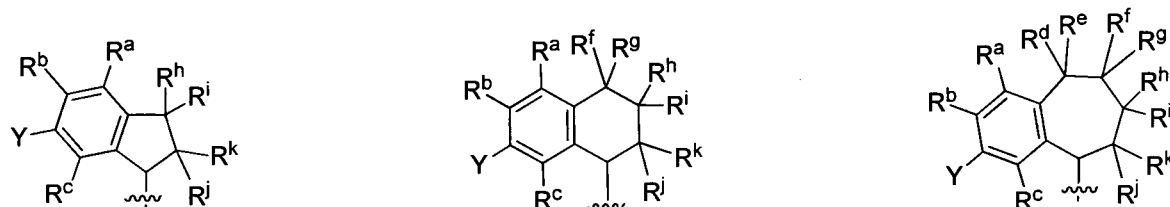


[00233] and the like, wherein the remaining groups such as R^f , R^g , R^h , R^i , R^j and R^k are independently selected from H, OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], and (2-6C)cyanoalkyl and R^1 is H, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], or (2-6C)cyanoalkyl.

[00234] In one embodiment of Formula I, Ring A is formula A-1.

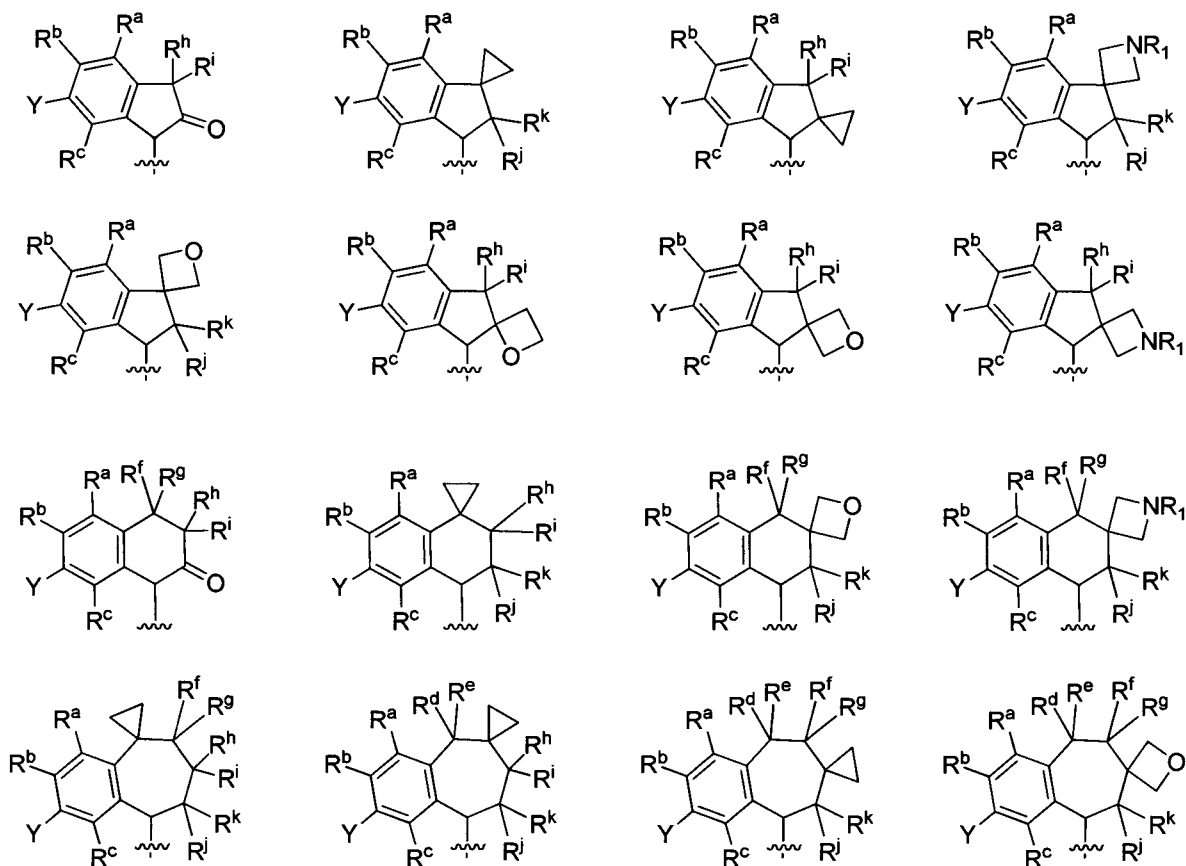
[00235] In one embodiment of Formula I, Ring A is formula A-1, where B is a bond or CR^dR^e , D is a bond or CR^fR^g , E is a bond or CR^hR^i , and F is CR^jR^k , provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms, where R^d , R^e , R^f , R^g , R^h , R^i , R^j , and R^k are as defined for Formula I.

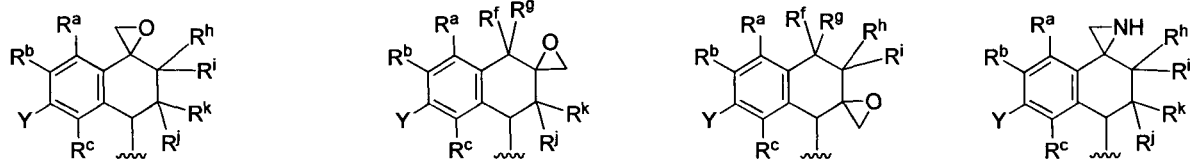
[00236] Examples of such ring systems include the structures:



[00237] where R^a , R^b , R^c , R^d , R^e , R^f , R^g , R^h , R^i , R^j , R^k and Y are as defined for Formula I. In one embodiment of Formula I, Ring A is formula A-1, where B is a bond or CR^dR^e , D is a bond or CR^fR^g , E is a bond or CR^hR^i , and F is CR^jR^k , provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains 5-6 atoms.

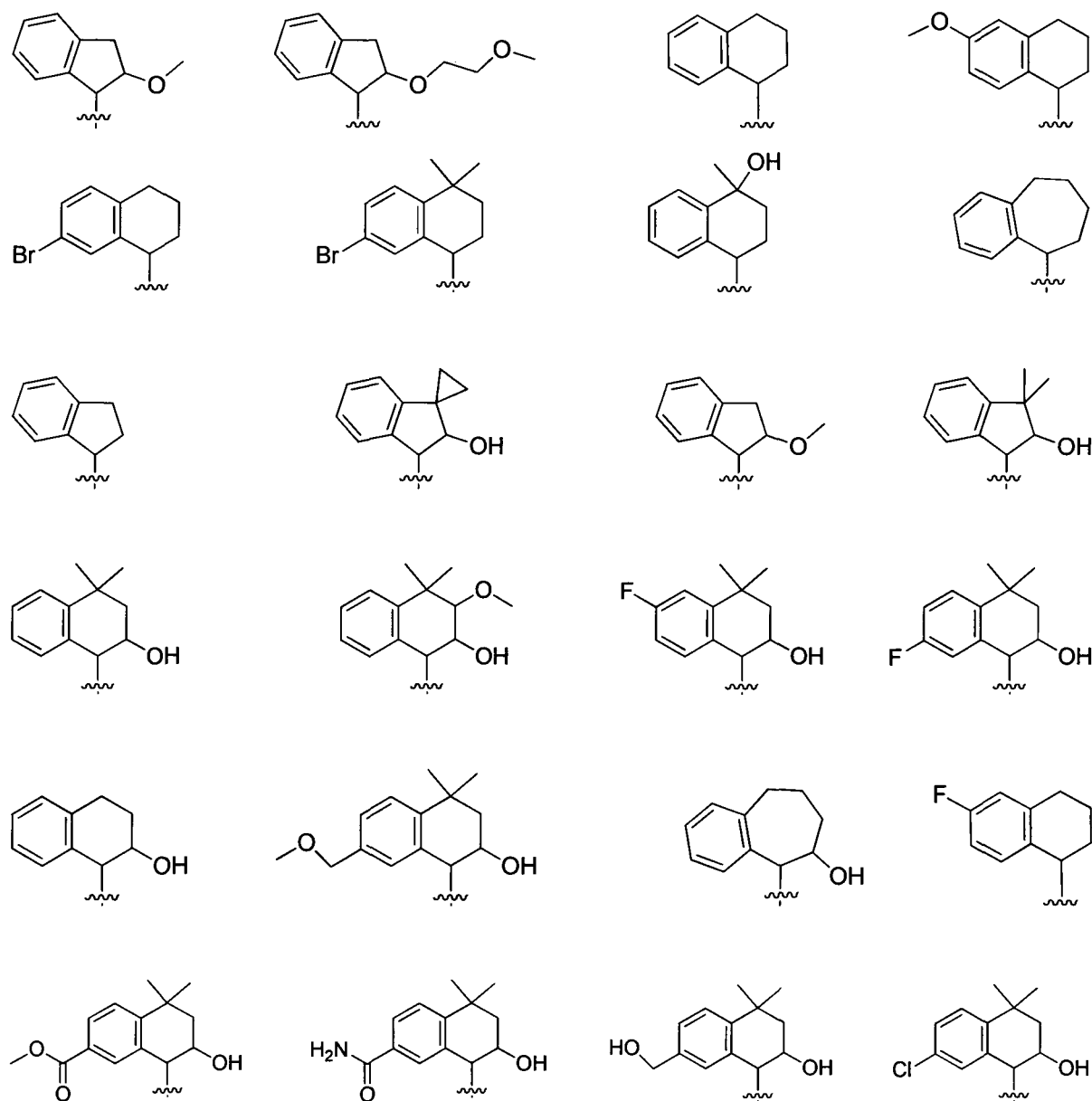
[00238] In one embodiment of Formula I, Ring A when represented by formula A-1 includes, but is not limited to, the following structures:

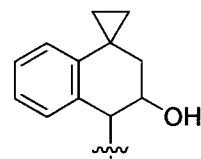
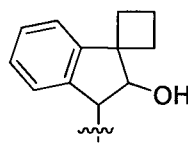
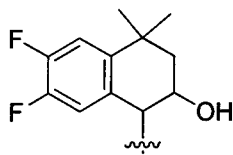
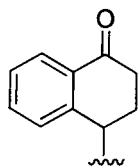




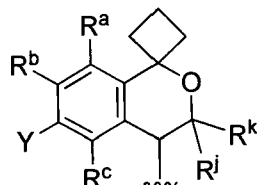
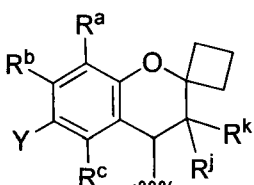
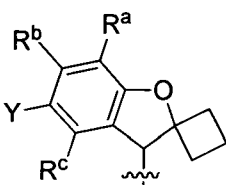
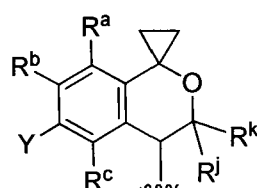
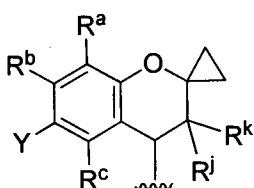
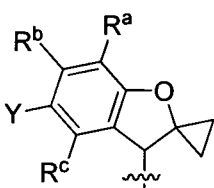
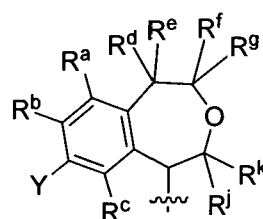
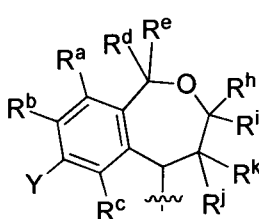
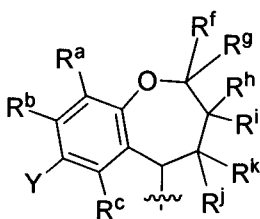
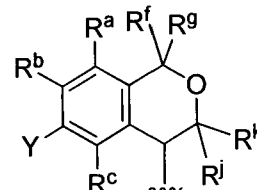
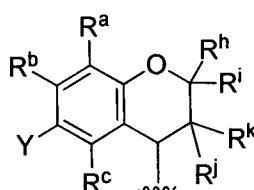
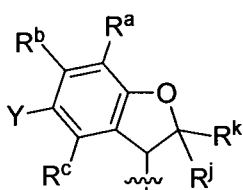
[00239] where R^a , R^b , R^c , R^d , R^e , R^f , R^g , R^h , R^i , R^j , R^k and Y are as defined for Formula I. In one embodiment of the above structures, R^a , R^b , R^c , R^d , R^e , R^f , R^g , R^h , R^i , R^j , R^k and Y are as defined for Formula I-2. In one embodiment of the above structures, and R^a , R^b , R^c , R^d , R^e , R^f , R^g , R^h , R^i , R^j , R^k and Y are as defined for Formula I-2.

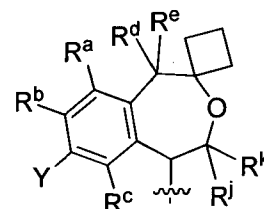
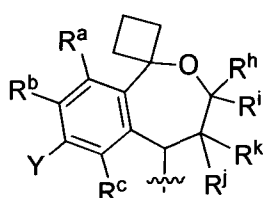
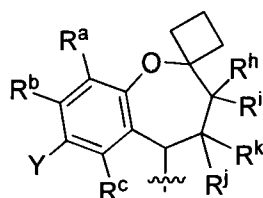
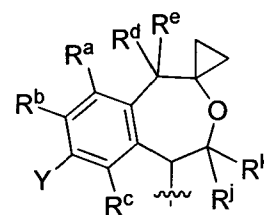
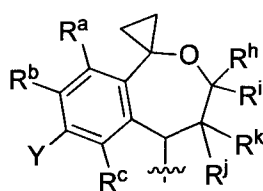
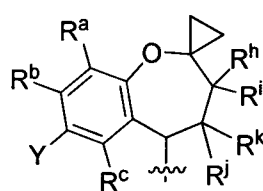
[00240] In one embodiment of Formula I, Ring A when represented by formula A-1 is selected from the structures:





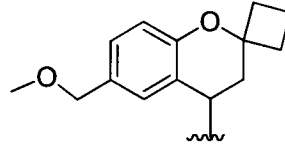
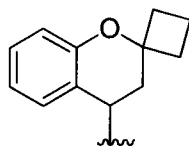
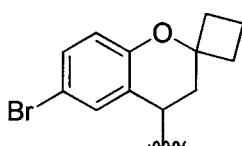
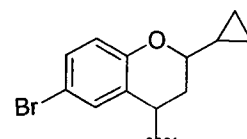
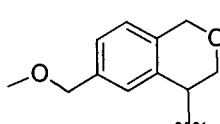
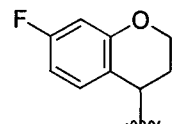
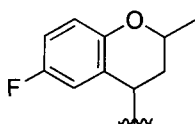
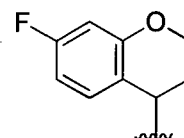
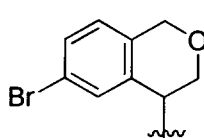
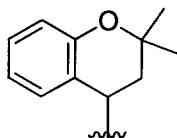
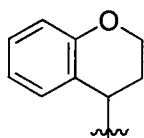
[00241] In one embodiment of Formula I, Ring A is A-1, wherein B is O, a bond or CR^dR^e ; D is O, a bond or CR^fR^g ; E is O, a bond or CR^hR^i ; and F is CR^jR^k , provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms and contains one oxygen atom, where R^d , R^e , R^f , R^g , R^h , R^i , R^j , and R^k are as defined for Formula I. Examples of such ring systems include, but are not limited to, the following structures:





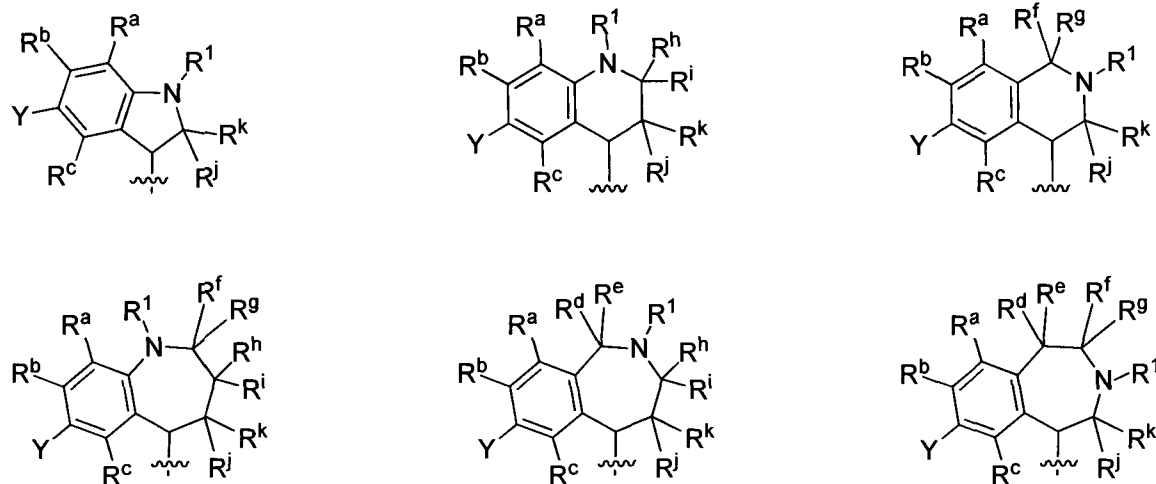
[00242] where R^a , R^b , R^c , R^d , R^e , R^f , R^g , R^h , R^i , R^j , R^k and Y are as defined for Formula I. In one embodiment of the above structures, and R^a , R^b , R^c , R^d , R^e , R^f , R^g , R^h , R^i , R^j , R^k and Y are as defined for Formula I-2.

[00243] In one embodiment of Formula I, Ring A when represented by formula A-1 is selected from the structures:



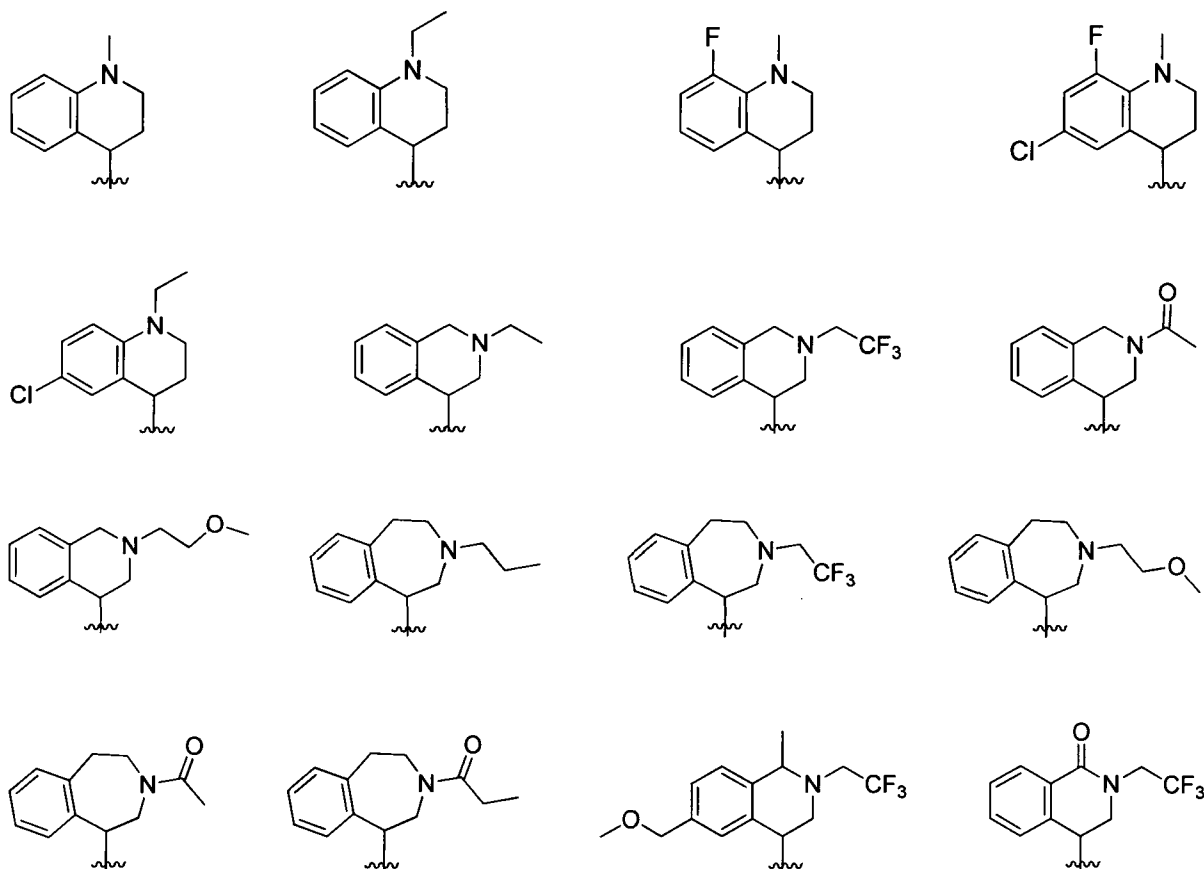
[00244] In one embodiment of Formula I, Ring A is formula A-1, wherein B is NR^1 , a bond or CR^dR^e ; D is NR^1 , a bond or CR^fR^g ; E is NR^1 , a bond or CR^hR^i ; and F is CR^jR^k , provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms and contains one nitrogen atom, where R^d , R^e , R^f , R^g , R^h , R^i , R^j , and R^k are as defined for Formula I.

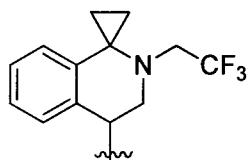
[00245] In one embodiment of Formula I, Ring A when represented by formula A-1 includes, but is not limited to, the following structures:



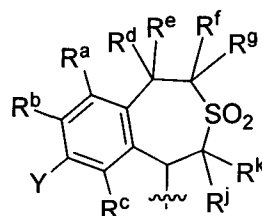
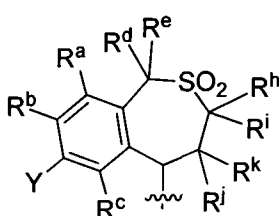
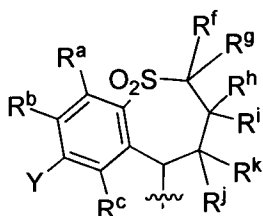
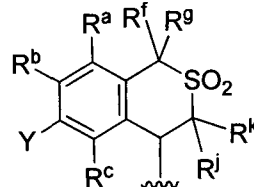
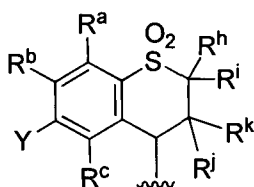
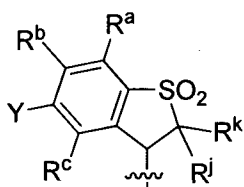
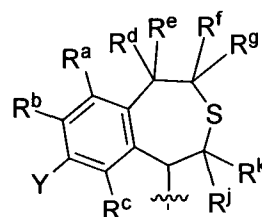
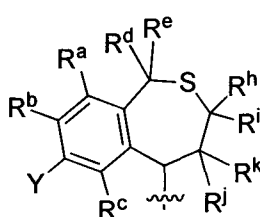
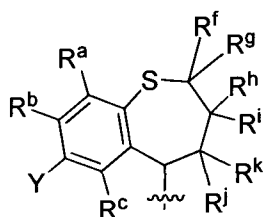
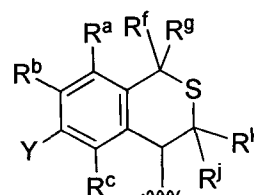
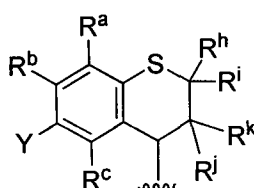
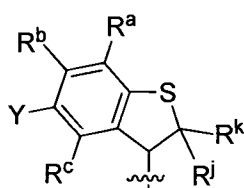
[00246] and the like, where R^1 , R^a , R^b , R^c , R^d , R^e , R^f , R^g , R^h , R^i , R^j , R^k and Y are as defined for Formula I. In one embodiment of the above structures, and R^a , R^b , R^c , R^d , R^e , R^f , R^g , R^h , R^i , R^j , R^k and Y are as defined for Formula I-2.

[00247] In one embodiment of Formula I, Ring A when represented by formula A-1 is selected from the structures:



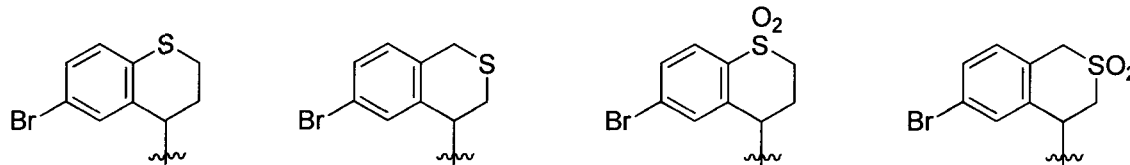


[00248] In one embodiment of Formula I, Ring A when represented by formula A-1 includes, but is not limited to, the following structures:



[00249] and the like, where R¹, R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k and Y are as defined for Formula I. In one embodiment of the above structures, and R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k and Y are as defined for Formula I-2.

[00250] In one embodiment of Formula I, Ring A when represented by formula A-1 is selected from the structures:



[00251] In one embodiment of Formula I, Ring A is formula A-1, wherein B is NR^1 or O; D is a bond or CR^fR^g ; E is a bond or CR^hR^i ; and F is CR^jR^k , provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms, where R^e , R^f , R^g , R^h , R^i , R^j , and R^k are as defined for Formula I.

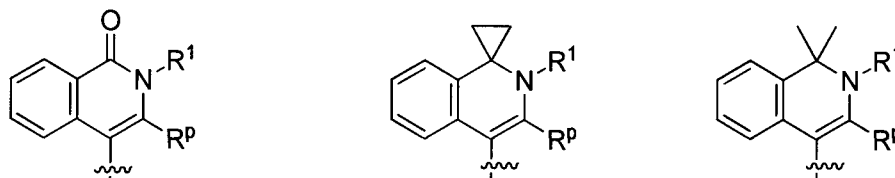
[00252] In one embodiment of Formula I, Ring A is formula A-1, wherein B is a bond or CR^dR^e ; D is NR^1 or O; E is a bond or CR^hR^i ; and F is CR^jR^k , provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms, where R^d , R^e , R^h , R^i , R^j , and R^k are as defined for Formula I.

[00253] In one embodiment of Formula I, Ring A is formula A-2, where G is CR^mR^n and K is NR^1 , and R^m , R^n , R^p and R^1 are as defined for Formula I.

[00254] In one embodiment of Formula I, Ring A is formula A-2, where G is CR^mR^n and K is NR^1 ; R^m is H, (1-3C)alkyl [optionally substituted with 1-5 fluoros], cyclopropyl or cyclobutyl; R^n is H or (1-3C)alkyl [optionally substituted with 1-5 fluoros]; and R^1 and R^p are as defined for Formula I.

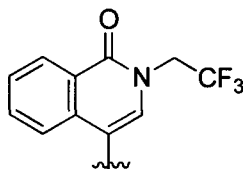
[00255] In one embodiment of Formula I, Ring A is formula A-2, where G is CR^mR^n and K is NR^1 ; R^m and R^n together form an oxo group; and R^1 and R^p are as defined for Formula I.

[00256] In one embodiment of Formula I, Ring A when represented by formula A-2 is selected from the structures:



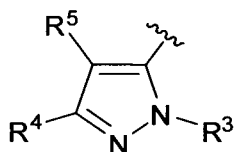
[00257] and the like, where R^1 and R^p are as defined for Formula I.

[00258] In one embodiment of Formula I, Ring A when represented by formula A-2



[00259] Reference will now be made to Ring C.

[00260] In one embodiment, Ring C is formula C-1:



C-1

[00261] where R³, R⁴ and R⁵ are as defined for Formula I.

[00262] In one embodiment, R³ is (1-6C)alkyl. In one embodiment, R³ is methyl or ethyl.

[00263] In one embodiment, R³ is hydroxy(1-6C)alkyl. An example of R³ is 2-hydroxyethyl.

[00264] In one embodiment, R³ is Ar², where Ar² is phenyl optionally substituted with one or more groups independently selected from halogen and (1-6C)alkyl.

[00265] In one embodiment, R³ when represented by Ar² is phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3-chlorophenyl, 3-chloro-4-fluorophenyl or 3-chloro-2-fluorophenyl. In one embodiment, R³ when represented by Ar² is phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methylphenyl, 3-methylphenyl or 4-methylphenyl. In one embodiment, R³ is phenyl.

[00266] In one embodiment, R³ is hetCyc¹, where hetCyc¹ is a 5-6-membered saturated or partially unsaturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O. In one embodiment, R³ is a pyrrolidinyl, tetrahydrofuranyl, imidazolidinyl, piperidinyl, piperazinyl, tetrahydropyranyl, or morpholinyl ring. In one embodiment, R³ is tetrahydro-2H-pyran-4-yl.

[00267] In one embodiment, R³ is (3-7C)cycloalkyl. In one embodiment R³ is cyclohexyl.

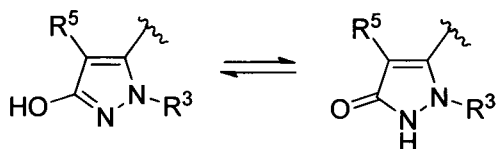
[00268] In one embodiment, R³ is hetAr², where hetAr² is 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more substituents independently selected from (1-6C)alkyl and halogen. In one embodiment, R³ is thienyl, furyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridyl, pyrimidyl, pyrazinyl, or pyridazinyl optionally substituted with one or more substituents independently selected from (1-6C)alkyl and halogen. In one embodiment, R³ is pyrazolyl, pyridyl or pyridazinyl optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen. In one embodiment, R³ is pyrazolyl, pyridyl or pyridazinyl optionally substituted with (1-6C)alkyl or

halogen. In one embodiment, R^3 when represented by hetAr^2 is 1-methyl-1H-pyrazol-4-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyridazinyl or 3-chloropyrid-5-yl.

[00269] In one embodiment, R^3 is selected from Ar^2 and hetAr^2 .

[00270] In one embodiment, R^3 is Ar^2 . In one embodiment, R^3 is phenyl.

[00271] In one embodiment, R^4 is OH. An examples of a C-1 ring when R^4 is OH includes the following tautomeric structures:



[00272] In one embodiment, R^4 is (1-6C)alkyl. In one embodiment, R^4 is methyl, ethyl, isopropyl or tert-butyl.

[00273] In one embodiment, R^4 is monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl or pentafluoro(2-6C)alkyl. In one embodiment, R^4 is fluoromethyl, 2-fluoroethyl, difluoromethyl and 2,2-difluoroethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 2,2,3,3-tetrafluoropropyl or 2,2,3,3,3-pentafluoropropyl.

[00274] In one embodiment, R^4 is trifluoro(1-6C)alkyl. In one embodiment, R^4 is CF_3 .

[00275] In one embodiment, R^4 is cyano(1-6C)alkyl. In one embodiment, R^4 is cyanomethyl or 2-cyanopropan-2-yl.

[00276] In one embodiment, R^4 is hydroxy(1-6C)alkyl. In one embodiment, R^4 is hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 2-hydroxy-2-methylpropyl or 1-hydroxy-2-methylpropan-2-yl.

[00277] In one embodiment, R^4 is dihydroxy(2-6C)alkyl. In one embodiment, R^4 is 2,3-dihydroxypropyl.

[00278] In one embodiment, R^4 is (1-3C alkoxy)(1-6C)alkyl. In one embodiment, R^4 is methoxymethyl, 2-methoxyethyl or 3-methoxypropyl.

[00279] In one embodiment, R^4 is amino(1-6C)alkyl. In one embodiment, R^4 is aminomethyl, 2-aminoethyl or 3-aminopropyl.

[00280] In one embodiment, R^4 is aminocarbonyl(1-6C)alkyl. In one embodiment, R^4 is aminocarbonylmethyl and 2-(aminocarbonyl)ethyl.

[00281] In one embodiment, R^4 is (1-3C)alkylsulfonamido(1-6C)alkyl. In one embodiment, R^4 is $\text{CH}_3\text{SO}_2\text{NHCH}_2-$ or $\text{CH}_3\text{SO}_2\text{NHCH}_2\text{CH}_2-$.

[00282] In one embodiment, R^4 is hydroxycarbonyl(1-6C)alkyl. In one embodiment, R^4 is $\text{HOC}(=\text{O})\text{CH}_2-$ and $\text{HOC}(=\text{O})\text{CH}_2\text{CH}_2-$.

[00283] In one embodiment, R^4 is $\text{hetAr}^3(1-6\text{C})\text{alkyl}$, where hetAr^3 is a 5-membered heteroaryl ring having 1-3 ring atoms independently selected from N, S and O and optionally substituted with (1-6C)alkyl. In one embodiment, hetAr^3 is a thienyl, furyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl or oxadiazolyl ring optionally substituted with (1-6C)alkyl. In one embodiment, R^4 when represented by $\text{hetAr}^3(1-6\text{C})\text{alkyl}$ is (1-methyl-1H-1,2,4-triazol-3-yl)methyl or (5-methyl-1,3,4-oxadiazol-2-yl)methyl.

[00284] In one embodiment, R^4 is $\text{Ar}^3(1-6\text{C})\text{alkyl}$, where phenyl optionally substituted with (1-4C)alkoxy or hydroxy(1-4C)alkyl. In one embodiment, $\text{Ar}^3(1-6\text{C})\text{alkyl}$ is benzyl.

[00285] In one embodiment, R^4 is (1-6C)alkoxy. Examples include methoxy and ethoxy.

[00286] In one embodiment, R^4 is monofluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, tetrafluoro(2-6C)alkoxy or pentafluoro(2-6C)alkoxy. In one embodiment, R^4 is fluoromethoxy, 2-fluoroethoxy, 2,2-difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy or 2,2-difluoroethoxy. In one embodiment, R^4 is 2-fluoroethoxy.

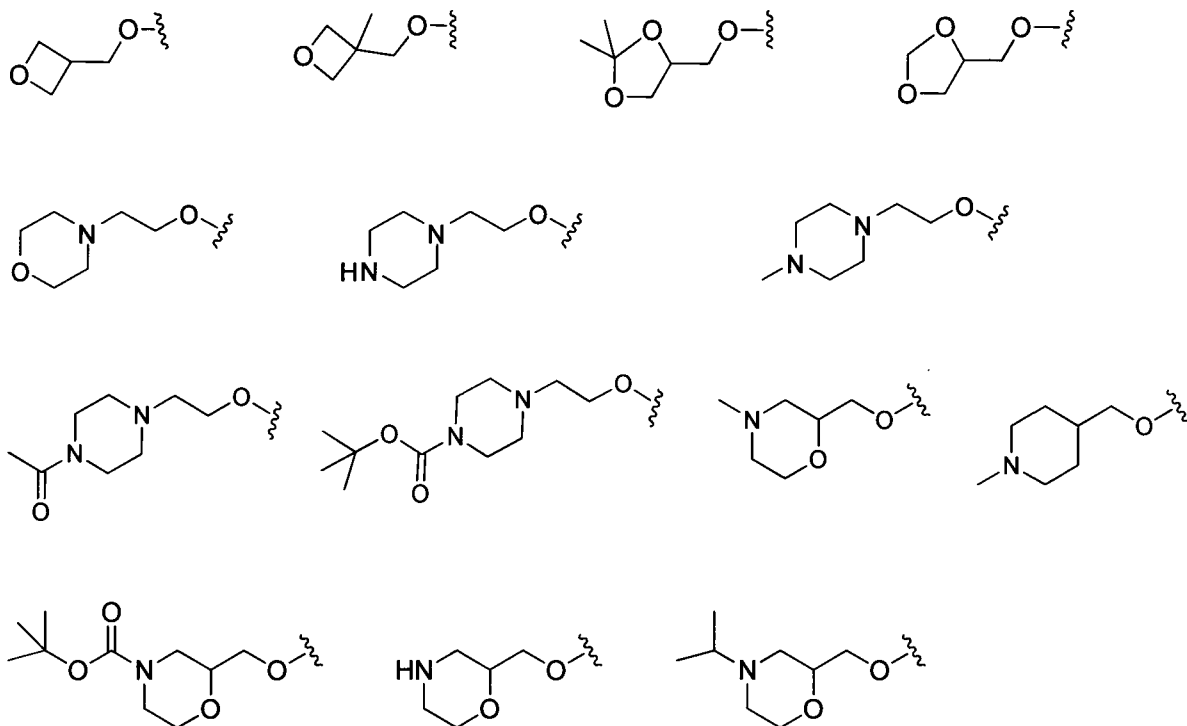
[00287] In one embodiment, R^4 is cyano(1-6C)alkoxy. In one embodiment, R^4 is cyanomethoxy or 2-cyanoethoxy.

[00288] In one embodiment, R^4 is hydroxy(1-6C)alkoxy. In one embodiment, R^4 is 2-hydroxy-2-methylpropoxy, 2-hydroxyethoxy, 2-hydroxypropoxy, 2-hydroxy-2-methylpropoxy or 2-hydroxybutoxy.

[00289] In one embodiment, R^4 is dihydroxy(2-6C)alkoxy. In one embodiment, R^4 is 2,3-dihydroxypropoxy or 3-hydroxy-2-(hydroxymethyl)propoxy.

[00290] In one embodiment, R^4 is amino(2-6C)alkoxy. In one embodiment, R^4 is $\text{H}_2\text{NCH}_2\text{CH}_2\text{O}-$ or $(\text{CH}_3)_3\text{NCH}_2\text{CH}_2\text{O}-$.

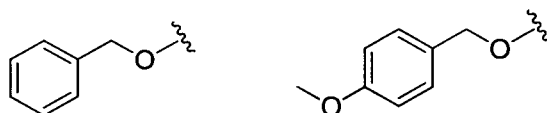
[00291] In one embodiment, R^4 is $\text{hetCyc}^2(1-6\text{C})\text{alkoxy}$, where hetCyc^2 is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O, wherein hetCyc^2 is optionally substituted with 1-2 groups independently selected from (1-6C)alkyl, (1-4C alkoxy)carbonyl, and (1-6C)acyl. In one embodiment, hetCyc^2 is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or 1,3-dioxolanyl optionally substituted with 1-2 groups independently selected from (1-6C)alkyl, (1-4C alkoxy)carbonyl and (1-6C)acyl. In one embodiment, R^4 when represented by $\text{hetCyc}^2(1-6\text{C})\text{alkoxy}$ is oxetan-2-ylmethoxy, 2-(oxetan-2-yl)propoxy, (2,2-dimethyl-1,3-dioxolan-4-yl)methoxy, (1,3-dioxolan-4-yl)methoxy, 2-morpholinoethoxy, 2-morpholinomethoxy, piperazinylethoxy, piperidinylethoxy or piperidinylmethoxy optionally substituted with 1-2 groups independently selected from (1-6C)alkyl, (1-4C alkoxy)carbonyl and (1-6C)acyl. In one embodiment, R^4 is represented by the structures:



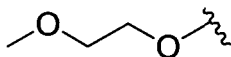
[00292] In one embodiment, R^4 is $\text{hetAr}^3(1-6\text{C})\text{alkoxy}$, where hetAr^3 is a 5-membered heteroaryl ring having 1-3 ring atoms independently selected from N, S and O and optionally substituted with (1-6C)alkyl. In one embodiment, hetAr^3 is a thienyl, furyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl or oxadiazolyl ring optionally substituted with (1-6C)alkyl. In one embodiment, hetAr^3 is triazolyl or oxadiazolyl ring optionally substituted with a (1-6C)alkyl group such as a methyl group. In one embodiment, R^4 when represented by $\text{hetAr}^3(1-6\text{C})\text{alkoxy}$ is (1-methyl-1H-1,2,4-triazol-3-yl)methoxy or (5-methyl-1,3,4-oxadiazol-2-yl)methoxy, which can be represented by the structures:



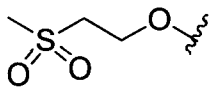
[00293] In one embodiment, R^4 is $\text{Ar}^3(1-6\text{C})\text{alkoxy}$, where Ar^3 is phenyl optionally substituted with (1-4C)alkoxy. In one embodiment, R^4 is phenylmethoxy or (4-methoxyphenyl)methoxy having the structures:



[00294] In one embodiment, R^4 is (1-4C alkoxy)(1-6C)alkoxy. In one embodiment, R^4 is (2-methoxy)ethoxy having the structure:



[00295] In one embodiment, R^4 is (1-3C alkylsulfonyl)(1-6C)alkoxy. In one embodiment, R^4 is (2-methylsulfonyl)ethoxy having the structure:

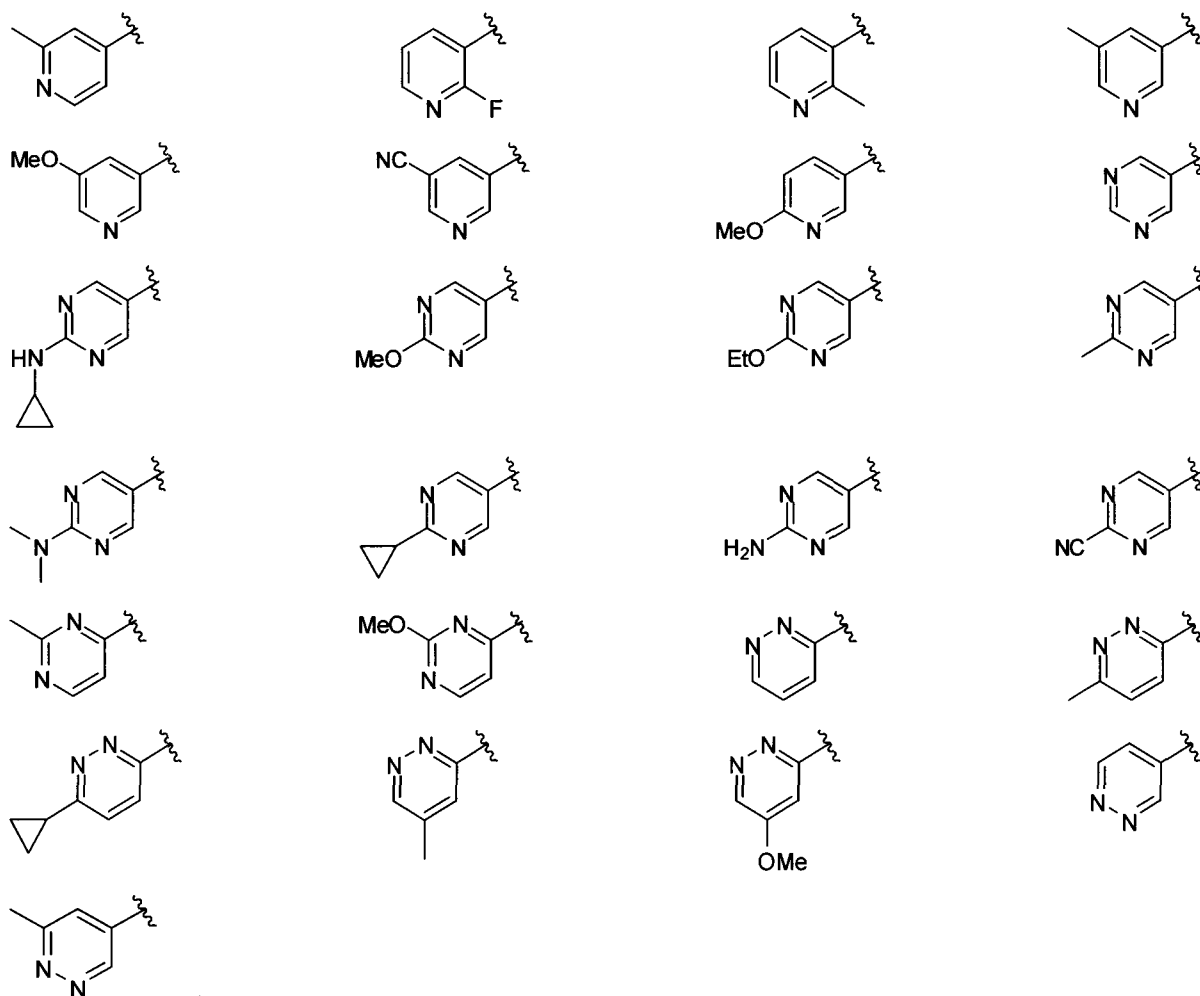


[00296] In one embodiment, R^4 is (3-6C)cycloalkyl optionally substituted with F, OH, (1-6C alkyl), (1-6C)alkoxy or (1-3C alkoxy)(1-6C)alkyl. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-hydroxycyclobutyl. In one embodiment, R^4 is cyclopropyl or 2-hydroxycyclobutyl. In one embodiment, R^4 is cyclopropyl.

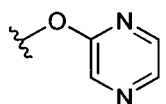
[00297] In one embodiment, R^4 is hetAr^4 , where hetAr^4 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with one or more substituents independently selected from (1-6C)alkyl, halogen, CN, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, difluoro(1-6C)alkyl, fluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH₂-, (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH₂, (1-6C alkyl)amino, di(1-6C alkyl)amino, (1-3C trifluoroalkoxy), fluoro(1-6C alkyl)amino, difluoro(1-6C alkyl)amino, trifluoro(1-6C alkyl)amino, and (3-4C cycloalkyl)amino.

[00298] In one embodiment, R^4 is hetAr^4 where hetAr^4 is pyridyl, pyrimidinyl, pyridazinyl, pyrazolyl, imidazolyl, thienyl, 1,2,4-triazolyl, 1,2,3-triazolyl, thiazolyl, oxazolyl, 1,3,4-oxadiazolyl, or 1,2,4-oxadiazolyl optionally substituted with one or more substituents independently selected from (1-6C)alkyl, halogen, CN, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, difluoro(1-6C)alkyl, fluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH₂-, (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH₂, (1-6C alkyl)amino, di(1-6C alkyl)amino, (1-3C trifluoroalkoxy), fluoro(1-6C alkyl)amino, difluoro(1-6C alkyl)amino, trifluoro(1-6C alkyl)amino, and (3-4C cycloalkyl)amino.

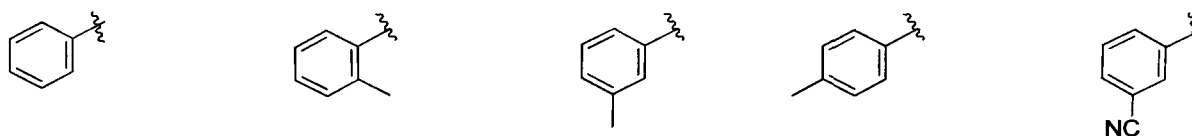
[00299] In one embodiment, R^4 is hetAr^4 where hetAr^4 is pyridyl, pyrimidinyl, pyridazinyl, pyrazolyl, imidazolyl, thienyl, 1,2,4-triazolyl, 1,2,3-triazolyl, thiazolyl, oxazolyl, 1,3,4-oxadiazolyl, or 1,2,4-oxadiazolyl optionally substituted with one or more substituents independently selected from (1-6C)alkyl, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH₂-, (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH₂, (1-6C alkyl)amino, di(1-6C alkyl)amino, (1-3C trifluoroalkoxy)(1-3C)trifluoroalkyl and cyclopropylNH-.

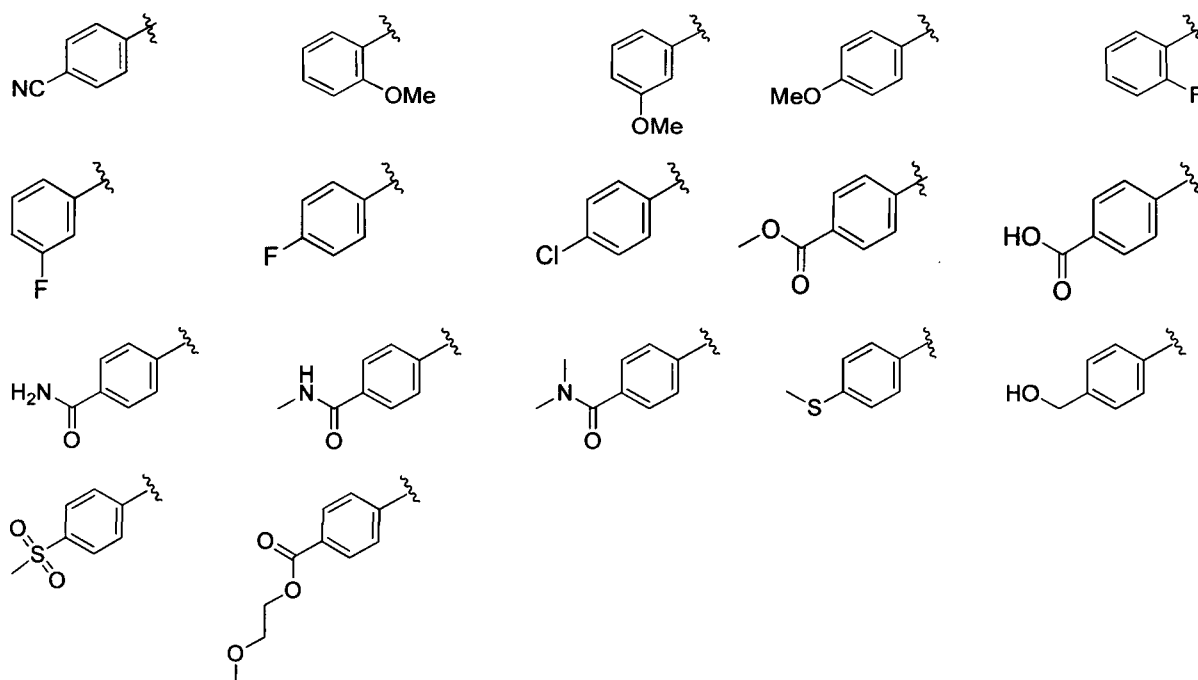


[00303] In one embodiment, R⁴ is hetAr⁴-O-. In one embodiment, R⁴ is the structure:

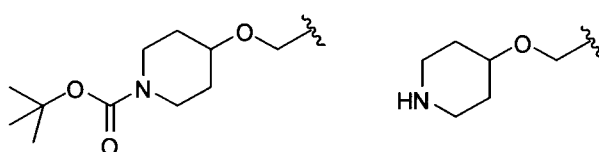


[00304] In one embodiment, R⁴ is Ar⁴, where Ar⁴ is phenyl optionally substituted with one or more groups independently selected from (1-6C)alkyl, halogen, CN, CF₃, CF₃O-, (1-6C)alkoxy, (1-6Calkyl)OC(=O)-, aminocarbonyl, (1-6C)alkylthio, hydroxy(1-6C)alkyl, (1-6C alkyl)SO₂-, HOC(=O)- and (1-3C alkoxy)(1-3C alkyl)OC(=O)-. In one embodiment, Ar⁴ is phenyl optionally substituted with one or more groups independently selected from methyl, F, Cl, CN, methoxy, CH₃OC(=O)-, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylthio, CH₃SO₂-, HOC(=O)- and CH₃OCH₂CH₂OC(=O)-. In one embodiment, Ar⁴ is phenyl optionally substituted with one or two of said substituents. In one embodiment, Ar⁴ is selected from the structures:





[00305] In one embodiment, R^4 is $\text{hetCyc}^2(\text{O})\text{CH}_2$, where hetCyc^2 is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O, wherein hetCyc^2 is optionally substituted with 1-2 groups independently selected from (1-6C)alkyl, (1-4C alkoxy)carbonyl, and (1-6C)acyl. Examples of hetCyc^2 include oxetaynyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, and 1,3-dioxolanyl rings optionally substituted with 1-2 groups independently selected from (1-6C)alkyl, (1-4C alkoxy)carbonyl and (1-6C)acyl. In one embodiment, R^4 when represented by $\text{hetCyc}^2(\text{O})\text{CH}_2$, is selected from the structures:

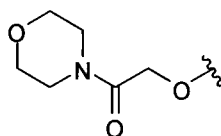


[00306] In one embodiment, R^4 is (1-4C alkoxy carbonyl)(1-6C)alkoxy. In one embodiment, R^4 is methoxycarbonyl(1-6C)alkoxy or ethylcarbonyl(1-6C)alkoxy. A particular example is ethoxycarbonylmethoxy.

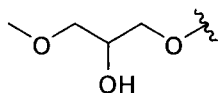
[00307] In one embodiment, R^4 is hydroxycarbonyl(1-6C)alkoxy. In one embodiment, R^4 is hydroxycarbonylmethoxy.

[00308] In one embodiment, R^4 is aminocarbonyl(1-6C)alkoxy. In one embodiment, R^4 is $\text{H}_2\text{NC}(=\text{O})(1-6\text{C})\text{alkoxy}$, $(1-6\text{C alkyl})\text{NHC}(=\text{O})(1-6\text{C})\text{alkoxy}$, or $\text{di}(1-6\text{Calkyl})\text{NC}(=\text{O})(1-6\text{C})\text{alkoxy}$. In one embodiment, R^4 is $\text{H}_2\text{NC}(=\text{O})\text{CH}_2\text{O}-$, $\text{H}_2\text{NC}(=\text{O})\text{CH}_2\text{CH}_2\text{O}$, or $\text{CH}_3\text{CH}_2\text{NC}(=\text{O})\text{CH}_2\text{O}-$.

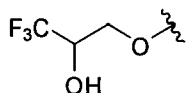
[00309] In one embodiment, R^4 is $\text{hetCyc}^2\text{C}(=\text{O})(1-6\text{C})\text{alkoxy}$, where hetCyc^2 is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with 1-2 groups independently selected from (1-6C)alkyl, (1-4C alkoxy)carbonyl, and (1-6C)acyl. In one embodiment, hetCyc^2 is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or 1,3-dioxolanyl optionally substituted with 1-2 groups independently selected from (1-6C)alkyl, (1-4C alkoxy)carbonyl and (1-6C)acyl. In one embodiment, hetCyc^2 is morpholinyl. In one embodiment, R^4 when represented by $\text{hetCyc}^2\text{C}(=\text{O})(1-6\text{C})\text{alkoxy}$ is the structure:



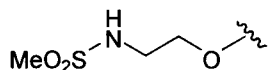
[00310] In one embodiment, R^4 is hydroxy(1-3C alkoxy)(1-6C)alkoxy. In one embodiment, R^4 is 2-hydroxy-3-methoxypropoxy, having the structure:



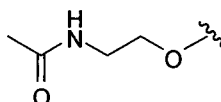
[00311] In one embodiment, R^4 is hydroxytrifluoro(1-6C)alkoxy. In one embodiment, R^4 is 3,3,3-difluoro-2-hydroxypropoxy having the structure:



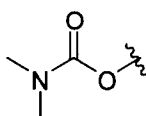
[00312] In one embodiment, R^4 is (1-3C)alkylsulfonamido(1-6C)alkoxy. In one embodiment, R^4 is methanesulfonamido(1-6C)alkoxy. In one embodiment, R^4 is 2-methanesulfonamidoethoxy having the structure:



[00313] In one embodiment, R^4 is (1-3C)alkylamido(1-6C)alkoxy. In one embodiment, R^4 is 2-(methylanido)ethoxy having the structure:

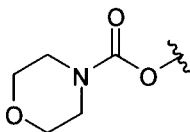


[00314] In one embodiment, R^4 is di(1-3C alkyl)aminocarboxy. In one embodiment, R^4 is dimethylaminocarboxy having the structure:



[00315] In one embodiment, R^4 is $\text{hetCyc}^2\text{C}(=\text{O})\text{O}-$, where hetCyc^2 is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and

optionally substituted with 1-2 groups independently selected from (1-6C)alkyl, (1-4C alkoxy)carbonyl and (1-6C)acyl. In one embodiment, hetCyc² is oxetaynyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or 1,3-dioxolanyl optionally substituted with 1-2 groups independently selected from (1-6C)alkyl, (1-4C alkoxy)carbonyl and (1-6C)acyl. In one embodiment, hetCyc² is morpholinyl. In one embodiment, R⁴ when represented by hetCyc²C(=O)O- is the structure:



[00316] In one embodiment, R⁴ is hydroxydifluoro(1-6C)alkyl. In one embodiment, R⁴ is 2,2-difluoro-2-hydroxyethyl.

[00317] In one embodiment, R⁴ is (1-4C alkylcarboxy)(1-6C)alkyl. In one embodiment, R⁴ is methylcarboxy(1-6C)alkyl. In one embodiment, R⁴ is 2-(methylcarboxy)ethyl.

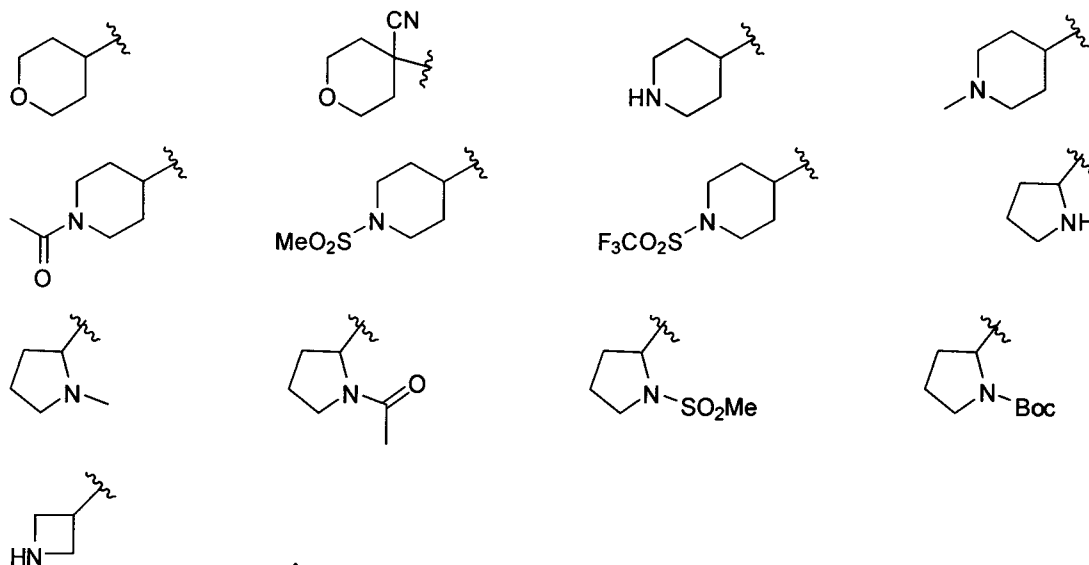
[00318] In one embodiment, R⁴ is (1-6C)alkoxycarbonyl. In one embodiment, R⁴ is methoxycarbonyl or ethoxycarbonyl.

[00319] In one embodiment, R⁴ is hydroxycarbonyl.

[00320] In one embodiment, R⁴ is aminocarbonyl, that is, a RR'NCO- radical where R and R' are independently hydrogen or (1-6C)alkyl as defined herein. In one embodiment, R⁴ is aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, ethylcarbonyl or isopropylaminocarbonyl.

[00321] In one embodiment, R⁴ is (1-3C alkoxy)aminocarbonyl. In one embodiment, R⁴ is methoxyaminocarbonyl.

[00322] In one embodiment, R⁴ is hetCyc³, where is a 4-7 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from F, CN, CF₃, (1-6C)alkyl, hydroxy(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-6C)acyl-, (1-6C)alkylsulfonyl, trifluoromethylsulfonyl and (1-4C alkoxy)carbonyl. In one embodiment, hetCyc³ is tetrahydropyranyl, piperidinyl, pyrrolidinyl or azetidiny optionally substituted with one or more substituents independently selected from F, CN, (1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-6C)acyl-, (1-6C)alkylsulfonyl, trifluoromethylsulfonyl and (1-4C alkoxy)carbonyl. In one embodiment, hetCyc³ is optionally substituted with one or two of said substituents. In one embodiment, hetCyc³ is tetrahydropyranyl, piperidinyl, pyrrolidinyl or azetidiny optionally substituted with CN, Me, CH₃C(=O)-, MeSO₂-, or CF₃SO₂-. In one embodiment, R⁴ when represented by hetCyc³ is selected from the structures:

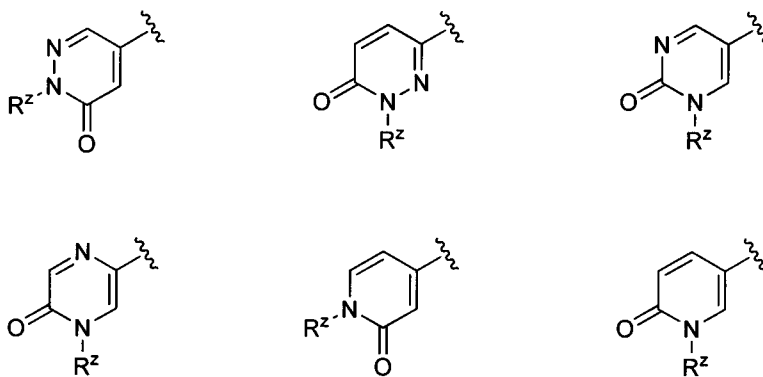


[00323] In one embodiment, R^4 is halogen. In one embodiment, R^4 is Br.

[00324] In one embodiment, R^4 is CN.

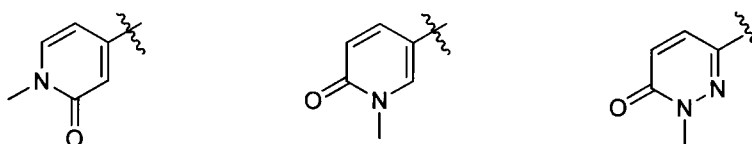
[00325] In one embodiment, R^4 is trifluoromethylsulfonyl.

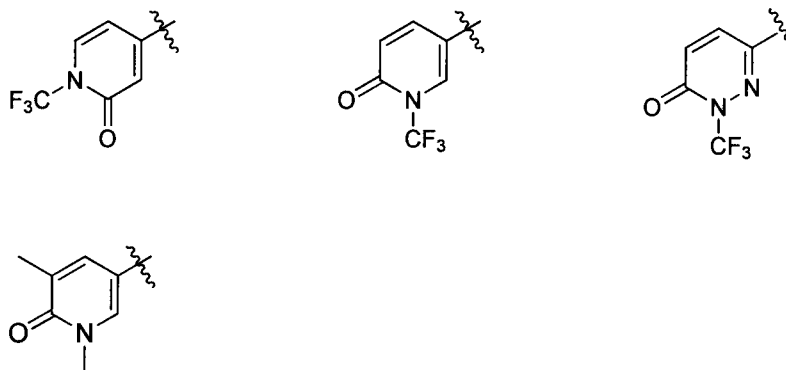
[00326] In one embodiment, R^4 is hetAr^5 , where hetAr^5 is a group selected from the structures:



[00327] where R^Z is (3-4C)cycloalkyl or (1-3C)alkyl (optionally substituted with 1-3 fluoros), wherein each of said hetAr^5 groups is optionally further substituted with one or more groups independently selected from F and (1-3C)alkyl optionally substituted with 1-3 fluoros.

[00328] In one embodiment, R^4 when represented by hetAr^5 is selected from the structures:





[00329] In one embodiment, R^4 is N-(1-3C alkyl)oxadiazolonyl. In one embodiment, R^4 is represented by the structures:

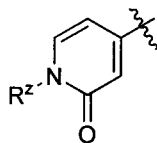


[00330] In one embodiment, R^4 is selected from H, (1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, cyano(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, monofluoro(1-6C)alkoxy, cyano(1-6C)alkoxy, hydroxy(1-6C)alkoxy, dihydroxy(2-6C)alkoxy, hetCyc²(1-6C)alkoxy, Ar³(1-6C)alkoxy, (1-4C alkoxy)(1-6C)alkoxy, (1-3C alkylsulfonyl)(1-6C)alkoxy, (3-6C)cycloalkyl, hetAr⁴, hetAr⁴-O-, Ar⁴, and hetAr⁵.

[00331] In one embodiment, R^4 is hetAr⁴, Ar⁴, or hetAr⁵.

[00332] In one embodiment, R^4 is hetAr⁴ or hetAr⁵.

[00333] In one embodiment, R^4 is pyrazolyl optionally substituted with one or more groups independently selected from (1-6C)alkyl, or a hetAr⁵ group having the structure:



[00334] where R^z is (3-4C)cycloalkyl or (1-3C)alkyl (optionally substituted with 1-3 fluoros), wherein said hetAr⁵ group is optionally further substituted with one or more groups independently selected from F and (1-3C)alkyl optionally substituted with 1-3 fluoros.

[00335] In one embodiment, R^5 is (1-6C)alkyl. In one embodiment, R^5 is methyl, ethyl, propyl, isopropyl or butyl.

[00336] In one embodiment, R^5 is monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl or pentafluoro(2-6C)alkyl. In one embodiment, R^5 is fluoromethyl, 2-fluoroethyl, difluoromethyl, 2,2-difluoroethyl, 1,3-difluoroprop-2-yl,

trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 1,1,2,2-tetrafluoropropane or 2,2,3,3,3-pentafluoropropyl.

[00337] In one embodiment, R^5 is halogen. In one embodiment, R^5 is F. In one embodiment, R^5 is Cl. In one embodiment, R^5 is Br.

[00338] In one embodiment, R^5 is CN.

[00339] In one embodiment, R^5 is (1-4C)alkoxy. In one embodiment, R^5 is methoxy or ethoxy.

[00340] In one embodiment, R^5 is hydroxy(1-4C)alkyl. In one embodiment, R^5 is hydroxymethyl or 3-hydroxypropyl.

[00341] In one embodiment, R^5 is (1-4C alkyl)OC(=O)-. In one embodiment, R^5 is $\text{CH}_3\text{CH}_2\text{OC}(=\text{O})-$.

[00342] In one embodiment, R^5 is (1-6C)alkylthio. In one embodiment, R^5 is methylthio (MeS-).

[00343] In one embodiment, R^5 is phenyl optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl and (1-6C)alkoxy. In one embodiment, R^5 is phenyl optionally substituted with one or more groups independently selected from F, Cl, methyl, ethyl, methoxy and ethoxy. In one embodiment, R^5 is phenyl.

[00344] In one embodiment, R^5 is (3-4C)cycloalkyl. In one embodiment, R^5 is cyclopropyl. In one embodiment, R^5 is cyclobutyl.

[00345] In one embodiment, R^5 is amino. In one embodiment, R^5 is NH_2 .

[00346] In one embodiment, R^5 is aminocarbonyl. In one embodiment, R^5 is $\text{H}_2\text{NC}(=\text{O})-$.

[00347] In one embodiment, R^5 is trifluoro(1-3C alkyl)amido. In one embodiment, R^5 is $\text{CF}_3\text{C}(=\text{O})\text{NH}-$.

[00348] In one embodiment, R^5 is halogen, CN, (1-6C)alkyl, (1-4C)alkoxy, hydroxy(1-4C)alkyl, or phenyl optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl and (1-6C)alkoxy.

[00349] In one embodiment, R^5 is selected from halogen, and (1-6C)alkyl.

[00350] In one embodiment, R^5 is selected from methyl, Cl and Br.

[00351] In one embodiment of Formula I, R^4 is selected from H, (1-6C)alkyl, trifluoro(1-6C)alkyl, cyano(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, cyano(1-6C)alkoxy, hydroxy(1-6C)alkoxy, (1-4C alkoxy)(1-6C)alkoxy, (3-6C)cycloalkyl, hetAr^4 , Ar^4 , and hetAr^5 ; and R^5 is selected from halogen, CN, (1-6C)alkyl, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-6C)alkylthio, and phenyl optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl and (1-6C)alkoxy.

[00352] In one embodiment of Formula I, R^4 is selected from hetAr^4 , Ar^4 , and hetAr^5 ; and R^5 is selected from (1-6C)alkyl.

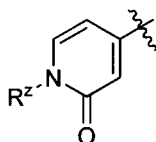
[00353] In one embodiment of Formula I, R^4 is selected from hetAr^4 and hetAr^5 ; and R^5 is selected from (1-6C)alkyl.

[00354] In one embodiment of Formula I, R^4 is hetAr^4 and R^5 is selected from (1-6C)alkyl.

[00355] In one embodiment of Formula I, R^4 is pyrazolyl optionally substituted with one or more substituents independently selected from (1-6C)alkyl; and R^5 is selected from (1-6C)alkyl.

[00356] In one embodiment of Formula I, R^4 is hetAr^5 ; and R^5 is selected from (1-6C)alkyl.

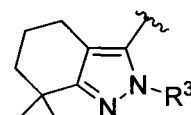
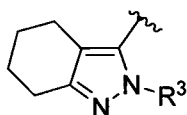
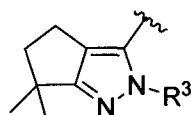
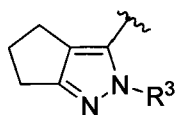
[00357] In one embodiment of Formula I, R^4 is a hetAr^5 group having the structure:

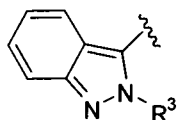


[00358] where R^z is (3-4C)cycloalkyl or (1-3C)alkyl (optionally substituted with 1-3 fluoros), wherein said hetAr^5 group is optionally further substituted with one or more groups independently selected from F and (1-3C)alkyl optionally substituted with 1-3 fluoros; and R^5 is selected from (1-6C)alkyl.

[00359] In one embodiment, R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated, partially unsaturated or unsaturated carbocyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl; or R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated, partially unsaturated or unsaturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or two substituents independently selected from (1-6C alkyl)C(=O)O-, (1-6C)acyl, (1-6C)alkyl and oxo, and said sulfur ring atom is optionally oxidized to S(=O) or SO₂.

[00360] In one embodiment, R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated, partially unsaturated or unsaturated carbocyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl. In one embodiment, Ring C when R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated or unsaturated carbocyclic ring is selected from the structures:

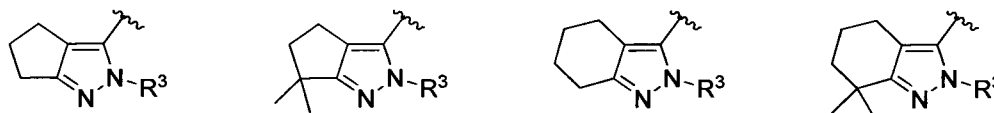




[00361] where R^3 is as defined for Formula I. In one embodiment of said structures, R^3 is phenyl.

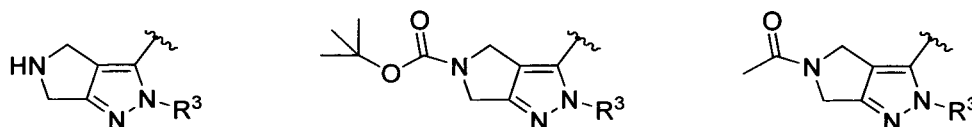
[00362] In one embodiment, R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated carbocyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl, or R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said ring nitrogen atom is optionally substituted with (1-6C alkyl)C(=O)O- or (1-6C)acyl, and said sulfur ring atom is optionally oxidized to S(=O) or SO₂.

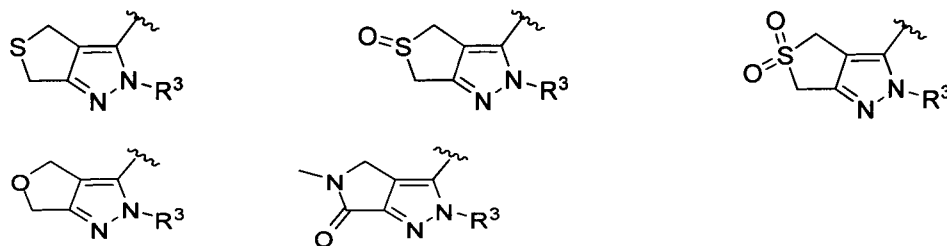
[00363] In one embodiment, R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated carbocyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl. In one embodiment, Ring C when R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated carbocyclic ring is selected from the structures:



[00364] where R^3 is as defined for Formula I. In one embodiment of said structures, R^3 is phenyl.

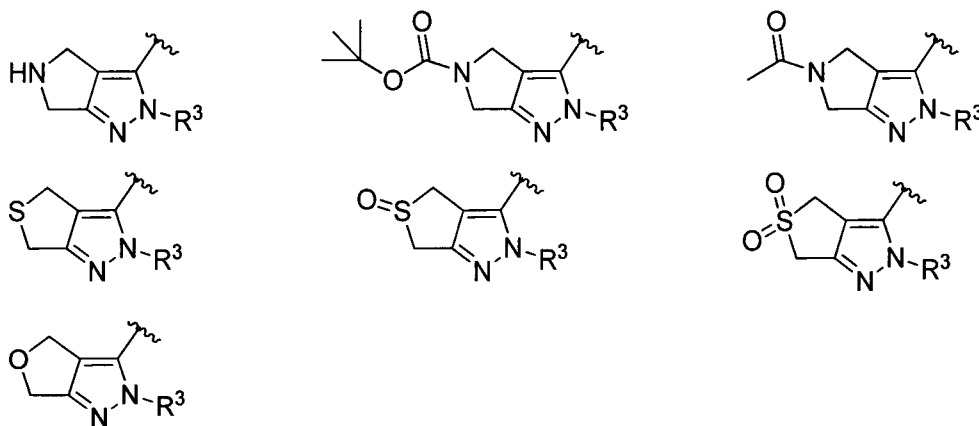
[00365] In one embodiment, R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated, partially unsaturated or unsaturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said ring N atom is optionally substituted with (1-6C alkyl)C(=O)O-, (1-6C alkyl)C(=O)-, (1-6C)alkyl or oxo, and said S ring atom is optionally oxidized to S(=O) or SO₂. In one embodiment, Ring C when R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated heterocyclic ring is selected from the structures:





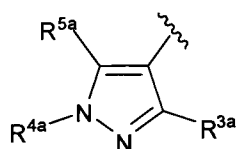
[00366] where R^3 is as defined for Formula I. In one embodiment of said structures, R^3 is phenyl.

[00367] In one embodiment, R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said ring N atom is optionally substituted with (1-6C alkyl)C(=O)O- or (1-6C alkyl)C(=O)-, and said S ring atom is optionally oxidized to S(=O) or SO₂. In one embodiment, Ring C when R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated heterocyclic ring is selected from the structures:



[00368] where R^3 is as defined for Formula I. In one embodiment of said structures, R^3 is phenyl.

[00369] In one embodiment, Ring C is formula C-2



C-2

[00370] where R^{3a} , R^{4a} and R^{5a} are as defined for Formula I. In one embodiment, R^{3a} , R^{4a} and R^{5a} are as defined for Formula I, with the exception that R^{3a} and R^{5a} are not hydrogen.

[00371] In one embodiment, R^{3a} is hydrogen.

[00372] In one embodiment, R^{3a} is halogen.

[00373] In one embodiment, R^{3a} is (1-6C)alkyl. In one embodiment, R^{3a} is methyl.

[00374] In one embodiment, R^{3a} is trifluoro(1-6C)alkyl. In one embodiment, R^{3a} is CF₃.

[00375] In one embodiment, R^{3a} is (3-6C)cycloalkyl. In one embodiment, R^{3a} is cyclopropyl.

[00376] In one embodiment, R^{3a} is phenyl optionally substituted with one or more substituents independently selected from halogen and (1-6C)alkyl. In one embodiment, R^{3a} is phenyl, fluorophenyl or methylphenyl, for example include phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3-chlorophenyl, 3-chloro-4-fluorophenyl or 3-chloro-2-fluorophenyl. In one embodiment, R^{3a} is phenyl.

[00377] In one embodiment, R^{3a} is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen. In one embodiment, R^{3a} is a thienyl, furyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridyl, pyrimidyl, pyrazinyl, or pyridazinyl ring optionally substituted with (1-6C)alkyl or halogen. In one embodiment, R^{3a} is pyrazolyl, pyridyl or pyridazinyl optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen. In one embodiment, R^{3a} is pyrazolyl, pyridyl or pyridazinyl optionally substituted with (1-6C)alkyl or halogen.

[00378] In one embodiment, R^{4a} is hydrogen.

[00379] In one embodiment, R^{4a} is (1-6C)alkyl. In one embodiment, R^{4a} is methyl, ethyl or isopropyl.

[00380] In one embodiment, R^{4a} is trifluoro(1-6C)alkyl. In one embodiment, R^{4a} is 2,2,2-trifluoroethyl.

[00381] In one embodiment, R^{4a} is phenyl optionally substituted with one or more groups independently selected from (1-6C)alkyl, halogen, CN, CF₃, CF₃O-, (1-6C)alkoxy, (1-6Calkyl)OC(=O)-, aminocarbonyl, (1-6C)alkylthio, hydroxy(1-6C)alkyl, (1-6C alkyl)SO₂-, HOC(=O)- and (1-3C alkoxy)(1-3C alkyl)OC(=O)-. In one embodiment, R^{4a} is phenyl optionally substituted with one or more groups independently selected from methyl, F, Cl, CN, methoxy, CH₃OC(=O)-, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylthio, CH₃SO₂-, HOC(=O)- or CH₃OCH₂CH₂OC(=O)-. In certain embodiments, R^{4a} is phenyl optionally substituted with one or two of said substituents. In one embodiment, R^{4a} is phenyl.

[00382] In one embodiment, R^{4a} is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with 1-2 substituents independently selected from (1-6C)alkyl, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH₂-, (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH₂, (1-6C alkyl)amino, di(1-6C alkyl)amino, and (1-3C trifluoroalkoxy)(1-3C)trifluoroalkyl. In one embodiment, R^{4a} is pyridyl, pyrimidinyl, pyridazinyl, pyrazolyl, imidazolyl, thionyl, 1,2,4-triazolyl, 1,2,3-triazolyl, thiazolyl, oxazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl or imidazo[1,2-a]pyridinyl optionally substituted with 1-2 substituents independently selected from (1-6C)alkyl, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH₂-, (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH₂, (1-6C alkyl)amino, di(1-6C alkyl)amino, and (1-3C trifluoroalkoxy)(1-3C)trifluoroalkyl. In one embodiment, R^{4a} is pyrazinyl.

[00383] In one embodiment, R^{5a} is as defined for Formula I.

[00384] In one embodiment, R^{5a} is selected from hydrogen, halogen, (1-6C)alkyl and phenyl.

[00385] In one embodiment, R^{5a} is hydrogen.

[00386] In one embodiment, R^{5a} is halogen.

[00387] In one embodiment, R^{5a} is (1-6C)alkyl. In one embodiment, R^{5a} is methyl.

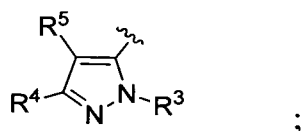
[00388] In one embodiment, R^{5a} is phenyl.

[00389] In one embodiment, Ring C is formula C-2, in which R^{3a} is (1-6C)alkyl, trifluoro(1-6C)alkyl or phenyl; R^{4a} is (1-6C)alkyl, trifluoro(1-6C)alkyl, phenyl or pyrazinyl; and R^{5a} is hydrogen, (1-6C)alkyl or phenyl.

[00390] In another embodiment of the present invention there is provided a compound according to Formula I, which is designated as Formula I-a, wherein:

[00391] X is O;

[00392] Ring C is C-1



C-1

[00393] R³ is (1-6C)alkyl, hydroxy(1-6C)alkyl, Ar², hetCyc¹, (3-7C)cycloalkyl, or hetAr²;

[00394] R⁴ is H, OH, (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, (1-3C)alkylsulfonamido(1-6C)alkyl, sulfamido(1-6C)alkyl,

hydroxycarbonyl(1-6C)alkyl, hetAr³(1-6C)alkyl, Ar³(1-6C)alkyl, (1-6C)alkoxy, monofluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy trifluoro(1-6C)alkoxy, tetrafluoro(2-6C)alkoxy, pentafluoro(2-6C)alkoxy cyano(1-6C)alkoxy, hydroxy(1-6C)alkoxy, dihydroxy(2-6C)alkoxy, amino(2-6C)alkoxy, hydroxyl-carbonyl(1-6C)alkoxy, hetCyc²(1-6C)alkoxy, hetAr³(1-6C)alkoxy, Ar³(1-6C)alkoxy, (1-4C alkoxy)(1-6C)alkoxy, (1-3C alkylsulfonyl)(1-6C)alkoxy, (3-6C)cycloalkyl [optionally substituted with F, OH, (1-6C alkyl), (1-6C) alkoxy, or (1-3C alkoxy)(1-6C)alkyl], hetAr⁴, hetAr⁴-O-, Ar⁴, hetCyc²(O)CH₂-, (1-4C alkoxycarbonyl)(1-6C)alkoxy, hydroxycarbonyl(1-6C)alkoxy, aminocarbonyl(1-6C)alkoxy, hetCyc²C(=O)(1-6C)alkoxy, hydroxy(1-3C alkoxy)(1-6C)alkoxy, hydroxytrifluoro(1-6C)alkoxy, (1-3C)alkylsulfonamido(1-6C)alkoxy, (1-3C)alkylamido(1-6C)alkoxy, di(1-3C alkyl)amino-carboxy, hetCyc²C(=O)O-, hydroxydifluoro(1-6C)alkyl, (1-4C alkylcarboxy)(1-6C)alkyl, (1-6C)alkoxycarbonyl, hydroxylcarbonyl, aminocarbonyl, (1-3C alkoxy)aminocarbonyl, hetCyc³, halogen, CN, trifluoromethylsulfonyl, N-(1-3C alkyl)oxadiazolonyl, or hetAr⁵;

[00395] R⁵ is (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-3C alkoxy)(1-4C)alkyl, (1-4C alkyl)OC(=O)-, or phenyl optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl and (1-6C)alkoxy; or

[00396] R⁴ and R⁵ together with the atoms to which they are attached form a 5-6 membered saturated, partially unsaturated or unsaturated carbocyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl, or

[00397] R⁴ and R⁵ together with the atoms to which they are attached form 5-6 membered saturated, partially unsaturated or unsaturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or two substituents independently selected from (1-6C alkyl)C(=O)O-, (1-6C)acyl, (1-6C)alkyl and oxo, and said sulfur ring atom is optionally oxidized to S(=O) or SO₂;

[00398] and

[00399] Ring A, Y, R^a, R^b, R^b, B, D, E, F, G, K, R¹, R^c, R^f, R^g, R^h, Rⁱ, R^j, R^k, R^m, R^m, R^p, Ar², hetCyc¹, hetCyc², hetCyc³, hetAr³, Ar³, hetAr⁴ hetAr⁵, and Ar⁴ are as defined for Formula I.

[00400] In one embodiment of Formula I-a, R⁴ is (1-6C)alkoxy, hetAr⁴, Ar⁴ or hetAr⁵; and Ring A, Y, R^a, R^b, R^b, B, D, E, F, G, K, R^p, R³, R⁵, Ar², hetAr⁴, Ar⁴, and hetAr⁵ are as defined for Formula I.

[00401] In one embodiment of Formula I-a, Ring A is formula A-1; B is a bond or CR^dR^e, D is a bond or CR^fR^g, E is a bond or CR^hRⁱ, and F is CR^jR^k, wherein the ring formed by B, D, E,

and F together with the atoms to which they are attached contains 5-6 atoms, and Y, R^a, R^b, R^b, R^p, R³, R⁴, R⁵, Ar², hetAr⁴, Ar⁴, and hetAr⁵ are as defined for Formula I.

[00402] In one embodiment of Formula I-a, R³ is Ar²; R⁴ is (1-6C)alkoxy, hetAr⁴, Ar⁴ or hetAr⁵; R⁵ is (1-6C)alkyl; and Ring A, Y, R^a, R^b, R^b, B, D, E, F, G, K, R¹, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, R^m, R^m, R^p, Ar², hetAr⁴, Ar⁴, and hetAr⁵ are as defined for Formula I. In one embodiment, R³ is phenyl.

[00403] In one embodiment of Formula I-a, R³ is Ar²; R⁴ is (1-6C)alkoxy, hetAr⁴ or hetAr⁵; R⁵ is (1-6C)alkyl; and Ring A, Y, R^a, R^b, R^b, B, D, E, F, G, K, R¹, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, R^m, R^m, R^p, Ar², hetAr⁴, and hetAr⁵ are as defined for Formula I. In one embodiment, R³ is phenyl.

[00404] In one embodiment of Formula I-a, R³ is Ar²; R⁴ is (1-6C)alkoxy or hetAr⁵; R⁵ is (1-6C)alkyl; and Ring A, Y, R^a, R^b, R^b, B, D, E, F, G, K, R¹, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, R^m, R^m, R^p, Ar², hetAr⁵ and Ar⁴ are as defined for Formula I. In one embodiment, R³ is phenyl.

[00405] In one embodiment of Formula I-a, R³ is Ar²; R⁴ is (1-6C)alkoxy or hetAr⁴; R⁵ is (1-6C)alkyl; Ring A is formula A-1; and Y, R^a, R^b, R^b, B, D, E, F, R¹, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, Ar², hetAr⁴ and Ar⁴ are as defined for Formula I. In one embodiment, R³ is phenyl.

[00406] In one embodiment of Formula I-a, R³ is Ar²; R⁴ is (1-6C)alkoxy or hetAr⁴; R⁵ is (1-6C)alkyl; Y is H; Ring A is formula A-1; B is a bond or CR^dR^e, D is a bond or CR^fR^g, E is a bond or CR^hRⁱ, and F is CR^jR^k, wherein the ring formed by B, D, E, and F together with the atoms to which they are attached contains 5-6 atoms, and R^a, R^b, R^b, R¹, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, Ar², hetAr⁴ and Ar⁴ are as defined for Formula I. In one embodiment, R³ is phenyl.

[00407] In one embodiment of Formula I-a, R³ is Ar²; R⁴ is (1-6C)alkoxy, hetAr⁴ or hetAr⁵; R⁵ is halogen or (1-6C)alkyl; Ring A is formula A-2; and Y, R^a, R^b, R^b, G, K, R¹, R^m, Rⁿ, R^p, Ar², hetAr⁴, and hetAr⁵ are as defined for Formula I. In one embodiment, R³ is phenyl.

[00408] In another embodiment of the present invention there is provided a compound according to Formula I, which is designated as Formula I-b, wherein:

[00409] X is O;

[00410] Ring A is formula A-1:

[00411] B is a bond or CR^dR^e,

[00412] D is a bond or CR^fR^g,

[00413] E is a bond or CR^hRⁱ, and

[00414] F is CR^jR^k,

[00415] provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms;

[00416] zero to four of R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], (1-6C)alkoxy [optionally substituted with one to five fluoros], or (1-3C alkoxy)(2-6C)alkoxy [optionally substituted with one to five fluoros],

[00417] or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring, or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k form an oxo group, and the remainder are hydrogen,

[00418] and wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom;

[00419] and R^a , R^b , R^c , Y and Ring C are as defined for Formula I. In a further embodiment of Formula I-b, Ring C is C-1. In a further embodiment of Formula I-b, R^4 is (1-6C)alkoxy, hetAr^4 or hetAr^5 . In a further embodiment of Formula I-b, R^3 is Ar^2 . In a further embodiment of Formula I-b, R^5 is halogen or (1-6C)alkyl. In a further embodiment of Formula I-b, Y is H, halogen, or (1-3C alkoxy)(1-6C)alkyl. In a further embodiment of Formula I-b, R^3 is phenyl.

[00420] In another embodiment of the present invention there is provided a compound according to Formula I, which is designated as Formula I-c, wherein:

[00421] X is O;

[00422] B is O, a bond or CR^dR^e ,

[00423] D is O, a bond or CR^fR^g ,

[00424] E is O, a bond or CR^hR^i , and

[00425] F is CR^jR^k ,

[00426] provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms and contains one oxygen atom;

[00427] zero to four of R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], (1-6C)alkoxy [optionally substituted with one to five fluoros], or (1-3C alkoxy)(2-6C)alkoxy [optionally substituted with one to five fluoros],

[00428] or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring, or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k form an oxo group, and the remainder are hydrogen,

[00429] and wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom;

[00430] and R^a , R^b , R^c , Y and Ring C are as defined for Formula I. In one embodiment, B is O, D is a bond or CR^fR^g , and E is a bond or CR^hR^i . In one embodiment, B is a bond or CR^dR^e , D is O, and E is a bond or CR^hR^i . In one embodiment, B is a bond or CR^dR^e , D is a bond or CR^fR^g , and E is O. In a further embodiment of Formula I-c, R^4 is (1-6C)alkoxy, $hetAr^4$ or $hetAr^5$. In a further embodiment of Formula I-c, R^3 is Ar^2 . In a further embodiment of Formula I-c, R^5 is halogen or (1-6C)alkyl. In a further embodiment of Formula I-c, Y is H, halogen or (1-3C alkoxy)(1-6C)alkyl. In a further embodiment of Formula I-c, R^3 is phenyl.

[00431] In another embodiment of the present invention there is provided a compound according to Formula I, which is designated as Formula I-d, wherein:

[00432] X is O;

[00433] B is NR^1 , a bond or CR^dR^e ,

[00434] D is NR^1 , a bond or CR^fR^g ,

[00435] E is NR^1 , a bond or CR^hR^i ,

[00436] F is CR^jR^k ,

[00437] provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms and contains one nitrogen atom;

[00438] zero to four of R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], (1-6C)alkoxy [optionally substituted with one to five fluoros], or (1-3C alkoxy)(2-6C)alkoxy [optionally substituted with one to five fluoros],

[00439] or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring, or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k form an oxo group, and the remainder are hydrogen,

[00440] and wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom;

[00441] and R^1 , R^a , R^b , R^c , Y and Ring C are as defined for Formula I. In one embodiment, B is NR^1 , D is a bond or CR^fR^g , and E is a bond or CR^hR^i . In one embodiment, B is a bond or CR^dR^e , D is NR^1 , and E is a bond or CR^hR^i . In one embodiment, B is a bond or CR^dR^e , D is a bond or CR^fR^g , and E is NR^1 . In a further embodiment of Formula I-d, R^4 is (1-6C)alkoxy, $hetAr^4$ or $hetAr^5$. In a further embodiment of Formula I-d, R^3 is Ar^2 . In a further embodiment of Formula I-d, R^5 is halogen or (1-6C)alkyl. In a further embodiment of Formula I-d, Y is H, halogen or (1-3C alkoxy)(1-6C)alkyl. In a further embodiment of Formula I-d, R^3 is phenyl.

[00442] In another embodiment of the present invention there is provided a compound according to Formula I, which is designated as Formula I-e, wherein:

[00443] X is O;

[00444] Ring A is formula A-2;

[00445] and G, K, Y, R^1 , R^m , R^n , R^p , and Ring C are as defined for Formula I. In a further embodiment of Formula I-e, Ring C is C-1. In a further embodiment of Formula I-e, R^4 is (1-6C)alkoxy, $hetAr^4$ or $hetAr^5$, and R^3 and R^5 are as defined for Formula I. In a further embodiment of Formula I-e, R^3 is Ar^2 , and R^5 is as defined for Formula I. In a further embodiment of Formula I-e, R^5 is (1-6C)alkyl. In a further embodiment of Formula I-e, R^p is H. In a further embodiment of Formula I-e, Y is H, halogen or (1-3C alkoxy)(1-6C)alkyl. In a further embodiment of Formula I-e, R^3 is phenyl.

[00446] In another embodiment of the present invention there is provided a compound according to Formula I, which is designated as Formula I-f, wherein:

[00447] X is O;

[00448] Ring A is formula A-2;

[00449] B is NR^1 or O, D is a bond or CR^fR^g , E is a bond or CR^hR^i , and F is CR^jR^k , provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms;

[00450] zero to four of R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros],

(1-6C)alkoxy [optionally substituted with one to five fluoros], or (1-3C alkoxy)(2-6C)alkoxy [optionally substituted with one to five fluoros],

[00451] or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring, or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k form an oxo group, and the remainder are hydrogen,

[00452] and wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom;

[00453] and R^1 , R^a , R^b , R^c , Y and Ring C are as defined for Formula I. In a further embodiment of Formula I-f, R^4 is (1-6C)alkoxy, hetAr⁴ or hetAr⁵. In a further embodiment of Formula I-f, R^3 is Ar². In a further embodiment of Formula I-f, R^5 is halogen or (1-6C)alkyl. In a further embodiment of Formula I-f, Y is H, halogen or (1-3C alkoxy)(1-6C)alkyl. In a further embodiment of Formula I-f, R^3 is phenyl.

[00454] In another embodiment of the present invention there is provided a compound according to Formula I, which is designated as Formula I-g, wherein:

[00455] X is O;

[00456] Ring A is formula A-2;

[00457] B is a bond or CR^dR^e ; D is NR^1 or O, E is a bond or CR^hR^i , and F is CR^jR^k , provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms;

[00458] zero to four of R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], (1-6C)alkoxy [optionally substituted with one to five fluoros], or (1-3C alkoxy)(2-6C)alkoxy [optionally substituted with one to five fluoros],

[00459] or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring, or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k form an oxo group, and the remainder are hydrogen,

[00460] and wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a

heteroatom, and only one of R^h and Rⁱ can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom;

[00461] and R¹, R^a, R^b, R^c, Y and Ring C are as defined for Formula I. In a further embodiment of Formula I-g, R⁴ is (1-6C)alkoxy, hetAr⁴ or hetAr⁵. In a further embodiment of Formula I-g, R³ is Ar². In a further embodiment of Formula I-g, R⁵ is halogen or (1-6C)alkyl. In a further embodiment of Formula I-g, Y is H, halogen or (1-3C alkoxy)(1-6C)alkyl. In a further embodiment of Formula I-g, R³ is phenyl.

[00462] It will be appreciated that certain compounds according to the invention may contain one or more centers of asymmetry and may therefore be prepared and isolated in a mixture of isomers such as a racemic mixture, or in an enantiomerically pure form.

[00463] It will further be appreciated that the compounds of Formula I or their salts may be isolated in the form of solvates, and accordingly that any such solvate is included within the scope of the present invention. For example, compounds of Formula I can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like.

[00464] The compounds of Formula I include pharmaceutically acceptable salts thereof. In addition, the compounds of Formula I also include other salts of such compounds which are not necessarily pharmaceutically acceptable salts, and which are useful as intermediates for preparing and/or purifying compounds of Formula I and/or for separating enantiomers of compounds of Formula I. Particular examples of salts include hydrochloride salts or trifluoroacetate salts.

[00465] In one embodiment, the compounds of Formula I include the free base form of compounds of Examples 1-160, or pharmaceutically acceptable salts thereof.

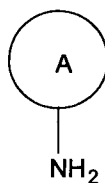
[00466] In one embodiment, the compounds of Formula I include the hydrochloride salts of compounds of Examples 1-160.

[00467] In one embodiment, the compounds of Formula I include the trifluoroacetate salts of compounds of Examples 1-160.

[00468] The term "pharmaceutically acceptable" indicates that the substance or composition is compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

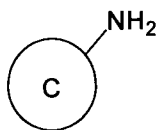
[00469] The present invention also provides a process for the preparation of a compound of Formula I or a salt thereof as defined herein, which comprises:

[00470] (a) for a compound of Formula I where X is O, coupling a corresponding compound having the formula II



II

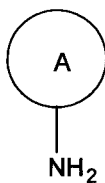
[00471] with a corresponding compound having the formula III



III

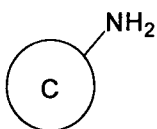
[00472] in the presence carbonyldiimidazole or triphosgene and a base; or

[00473] (b) for a compound of Formula I where X is S, coupling a corresponding compound having the formula II



II

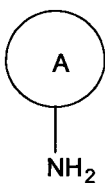
[00474] with a corresponding compound having the formula III



III

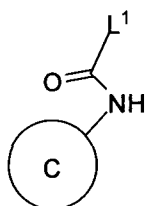
[00475] in the presence di(1H-imidazol-2-yl)methanethione and a base; or

[00476] (c) for a compound of Formula I where X is O, coupling a corresponding compound having the formula II



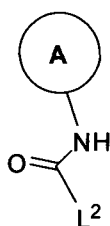
II

[00477] with a corresponding compound having the formula IV

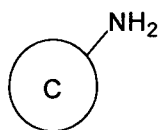
**IV**

[00478] where L^1 is a leaving group, in the presence of a base; or

[00479] (d) for a compound of Formula I where X is O, coupling a corresponding compound having the formula V

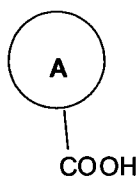
**V**

[00480] where L^2 is a leaving group, with a corresponding compound having the formula III

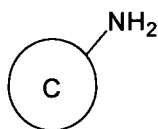
**III**

[00481] in the presence of a base; or

[00482] (e) for a compound of Formula I where X is O, activating a corresponding compound having the formula VI

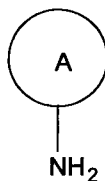
**VI**

[00483] with diphenylphosphoryl azide followed by coupling the activated intermediate with a corresponding compound having the formula III

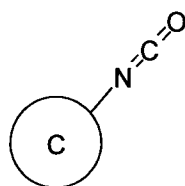
**III**

[00484] in the presence of a base; or

[00485] (f) for a compound of Formula I where X is O, coupling a corresponding compound having the formula II

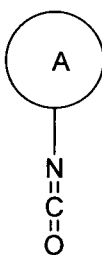
**II**

[00486] with a corresponding compound having the formula VII

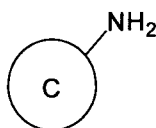
**VII**

[00487] in the presence of a base; or

[00488] (g) for a compound of Formula I where X is O, coupling a corresponding compound having the formula VIII

**VIII**

[00489] with a corresponding compound having the formula III

**III**

[00490] in the presence of a base; and

[00491] optionally removing protecting groups and optionally preparing a pharmaceutically acceptable salt thereof.

[00492] In the above methods, the term "corresponding" means that the definitions for the "corresponding compound" are as defined for Formula I unless stated otherwise.

[00493] Referring to method (a), the base may be an amine base, such as triethylamine or diisopropylethylamine. Suitable solvents include dichloromethane, dichloroethane, THF, DMA and DMF. The reaction is conveniently performed at ambient temperature.

[00494] Referring to method (b), the base may be an amine base, such as triethylamine or diisopropylethylamine. Suitable solvents include dichloromethane, dichloroethane, THF, DMA and DMF. The reaction is conveniently performed at ambient temperature.

[00495] Referring to method (c), the leaving group may be, for example, phenoxy or 4-nitrophenoxy. The base may be an amine base, such as triethylamine or diisopropylethylamine. Suitable solvents include DMA, DMF and DCE. The reaction is conveniently performed at ambient temperature.

[00496] Referring to method (d), the leaving group may be, for example, phenoxy or 4-nitrophenoxy. The base may be an amine base, such as triethylamine or diisopropylethylamine. Suitable solvents include DCE, DMA and DMF. The reaction is conveniently performed at ambient temperature.

[00497] Referring to method (e), the base may be an amine base, such as triethylamine or diisopropylethylamine. Suitable solvents include toluene and DMF. The reaction is conveniently performed at elevated temperatures, for example the reflux temperature of the solvent.

[00498] Referring to methods (f) and (g), the base may be an amine base, such as triethylamine or diisopropylethylamine. Suitable solvents include DCM, DCE, DMF and THF. The reaction is conveniently performed at temperatures between about 0 °C and ambient temperature.

[00499] Amine groups in compounds described in any of the above methods may be protected with any convenient amine protecting group, for example as described in Greene & Wuts, eds., "Protecting Groups in Organic Synthesis", 2nd ed. New York; John Wiley & Sons, Inc., 1991. Examples of amine protecting groups include acyl and alkoxycarbonyl groups, such as t-butoxycarbonyl (BOC), benzyloxycarbonyl (Cbz), and [2-(trimethylsilyl)ethoxy]methyl (SEM). Likewise, carboxyl groups may be protected with any convenient carboxyl protecting group, for example as described in Greene & Wuts, eds., "Protecting Groups in Organic Synthesis", 2nd ed. New York; John Wiley & Sons, Inc., 1991. Examples of carboxyl protecting groups include (1-6C)alkyl groups, such as methyl, ethyl and t-butyl. Alcohol groups may be protected with any convenient alcohol protecting group, for example as described in Greene & Wuts, eds., "Protecting Groups in Organic Synthesis", 2nd ed. New York; John Wiley & Sons, Inc., 1991. Examples of alcohol protecting groups include acetyl, benzyl, trityl, silyl ethers, and the like.

[00500] The compounds of the formulas **II**, **III**, **IV**, **V**, **VI**, **VII** and **VIII** are also provided as further aspects of the invention. In one embodiment, the compounds of the formulas

II, III, IV, V, VI, VII and VIII are useful as intermediates for the preparation of compounds of Formula **I**.

[00501] Compounds of Formula **I** are useful in the treatment of pain, cancer, inflammation/inflammatory diseases, neurodegenerative diseases, certain infectious diseases, Sjogren's syndrome, endometriosis, diabetic peripheral neuropathy, prostatitis or pelvic pain syndrome.

[00502] In one embodiment, compounds of Formula **I** are useful for treating pain, including chronic and acute pain. For example, compounds of Formula **I** are useful in the treatment of multiple types of pain including inflammatory pain, neuropathic pain, and pain associated with cancer, surgery or bone fracture.

[00503] In one embodiment, compounds of Formula **I** are useful for treating acute pain. Acute pain, as defined by the International Association for the Study of Pain, results from disease, inflammation, or injury to tissues. This type of pain generally comes on suddenly, for example, after trauma or surgery, and may be accompanied by anxiety or stress, and is confined to a given period of time and severity. In some instances, it can become chronic.

[00504] In one embodiment, compounds of Formula **I** are useful for treating chronic pain. Chronic pain, as defined by the International Association for the Study of Pain, is widely believed to represent a disease in itself. It can be made much worse by environmental and psychological factors. Chronic pain persists over a longer period than acute pain and is resistant to most medical treatments, generally over 3 months or more. It can and often does cause severe problems for patients.

[00505] Compounds of Formula **I** are also useful for treating cancer. Particular examples include neuroblastoma, ovarian, pancreatic, colorectal and prostate cancer.

[00506] Compounds of Formula **I** are also useful for treating inflammation and certain infectious diseases. For example, compounds of Formula **I** may be used to treat interstitial cystitis (IC), painful bladder syndrome (PBS), urinary incontinence, asthma, atopic dermatitis, and psoriasis.

[00507] Compounds of Formula **I** are also useful for treating a neurodegenerative disease in a mammal, comprising administering to said mammal one or more compounds of Formula **I** or a pharmaceutically acceptable salt thereof in an amount effective to treat said neurodegenerative disease. In one embodiment, compounds of Formula **I** may also be used to treat demyelination and dysmyelination by promoting myelination, neuronal survival, and oligodendrocyte differentiation via blocking Sp35-TrkA interaction. In one embodiment, the neurodegenerative disease is multiple sclerosis. In one embodiment, the neurodegenerative

disease is Parkinson's disease. In one embodiment, the neurodegenerative disease is Alzheimer's disease.

[00508] Compounds of Formula I are also useful for treating certain infectious diseases such as *Trypanosoma cruzi* infection in a mammal.

[00509] Compounds of Formula I are also useful for treating Sjogren's syndrome in a mammal.

[00510] Compounds of Formula I are also useful for treating endometriosis in a mammal.

[00511] Compounds of Formula I are also useful for treating diabetic peripheral neuropathy in a mammal.

[00512] Compounds of Formula I are also useful for treating prostatitis in a mammal.

[00513] Compounds of Formula I are also useful for treating pelvic pain syndrome in a mammal.

[00514] Compounds of Formula I are also useful in treating diseases related to an imbalance of the regulation of bone remodeling, such as osteoporosis, rheumatoid arthritis, and bone metastases.

[00515] As used herein, terms "treat" or "treatment" refer to therapeutic or palliative measures. Beneficial or desired clinical results include, but are not limited to, alleviation, in whole or in part, of symptoms associated with a disorder or condition, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

[00516] In certain embodiments, compounds of Formula I are useful for preventing diseases and disorders as defined herein. The term "preventing" as used herein means the prevention of the onset, recurrence or spread, in whole or in part, of the disease or condition as described herein, or a symptom thereof, and includes to the administration of a compound of Formula I prior to the onset of symptoms.

[00517] Accordingly, one embodiment of this invention provides a method of treating pain in a mammal, comprising administering to said mammal in need thereof one or more compounds of Formula I or a pharmaceutically acceptable salt thereof in an amount effective to treat said pain. In one embodiment, the pain is chronic pain. In one embodiment, the pain is acute pain. In one embodiment, the pain is inflammatory pain, neuropathic pain, or pain associated with cancer, surgery, or bone fracture.

[00518] Another embodiment of this invention provides a method of preventing pain in a mammal, comprising administering to said mammal in need thereof one or more compounds of Formula I or a pharmaceutically acceptable salt thereof in an amount effective to prevent said pain. In one embodiment, the pain is chronic pain. In one embodiment, the pain is acute pain. In one embodiment, the pain is inflammatory pain, neuropathic pain, or pain associated with cancer, surgery, or bone fracture.

[00519] Another embodiment of this invention provides a method of treating cancer in a mammal, comprising administering to said mammal in need thereof one or more compounds of Formula I or a pharmaceutically acceptable salt thereof in an amount effective to treat said cancer.

[00520] In one embodiment, provided herein is a method for treating a patient diagnosed with a cancer having a dysregulation of TrkA, comprising administering to the patient a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof.

[00521] In one embodiment, the dysregulation of TrkA comprises overexpression of wild-type TrkA (autocrine activation).

[00522] In one embodiment, the dysregulation of TrkA comprises one or more chromosome translocations or inversions resulting in TrkA gene fusions. In one embodiment, the dysregulation is a result of genetic translocations in which the expressed protein is a fusion protein containing residues from non-TrkA and TrkA proteins, and at a minimum the TrkA kinase domain. In one embodiment, the TrkA fusion protein is LMNA-TrkA, TFG-TrkA, TPM3-TrkA, CD74-TrkA, NFASC-TrkA, MPRIP-TrkA, BCAN-TrkA, or TPR-TrkA, where:

LMNA	=	Prelamin-A/C;
TFG	=	TRK-fused gene protein;
TPM3	=	Tropomyosin alpha-3;
CD74	=	HLA class II histocompatibility antigen gamma chain;
NFASC	=	Neurofascin;
MPRIP	=	MPRIP protein;
BCAN	=	Brevican core protein; and
TPR	=	Nucleoprotein TPR

[00523]

[00524] In one embodiment, the dysregulation of TrkA comprises one or more deletions, insertions or mutations in the TrkA protein. In one embodiment, the dysregulation comprises a deletion of one or more residues from the TrkA protein, resulting in constitutive activity of TrkA

kinase. In one embodiment the deletion includes deletion of residues 303-377 in TrkA Isoform 2.

[00525] In one embodiment, the dysregulation of TrkA comprises a splice variation in which the expressed protein is an alternatively spliced variant of TrkA having one or more residues deleted resulting in constitutive activity of TrkA kinase. In one embodiment, an alternatively spliced form of TrkA with constitutive activity has deletions of exons 8, 9, and 11 resulting in an expressed protein missing residues 192-284 and 393-398 relative to TrkA Isoform 2.

[00526] Cancers identified as having dysregulation of TrkA (see literature references below; also see www.cancer.gov and www.nccn.org) include:

[00527] (A) Cancers wherein the dysregulation of TrkA comprises one or more chromosome translocations or inversions resulting in TrkA gene fusions, including:

[00528]

Cancer	Literature reference(s)	Standard of Care
Non-Small Cell Lung Cancer	Vaishnavi et al. 2013: Nature Medicine 19, 1469-1472	radiotherapy (e.g. radioiodide therapy, external-beam radiation, radium 223 therapy), chemotherapeutics as single agents (e.g. afatinib dimaleate, bevacizumab, carboplatin, cetuximab, cisplatin, crizotinib, erlotinib, gefitinib, gemcitabine, methotrexate, paclitaxel, pemetrexed) or combinations (e.g. carboplatin-paclitaxel, gemcitabine-paclitaxel, chemoradiation)
Papillary Thyroid Carcinoma	Caria et al. 2010: Cancer Genetics and Cytogenetics 203:21-29	Radiotherapies (e.g. radioiodide therapy, external-beam radiation) and chemotherapeutics (e.g. sorafenib, sunitinib, pazopanib)
Glioblastoma Multiforme	Frattini et al. 2013: Nature Genet. 45(10):1141-9	Chemotherapeutics (e.g. bevacizumab, everolimus, lomustine, temozolomide)
Colorectal Carcinoma	Martin-Zanca et al. 1986: Nature 319:743	Chemotherapeutics as single agents (afibercept, bevacizumab, capecitabine,

Cancer	Literature reference(s)	Standard of Care
		cetuximab, fluorouracil, irinotecan, leucovorin, oxaliplatin, panitumumab, regorafenib) or combinations (e.g. folfox, folfiri, capox, folfiri-bevacizumab, folfiri-cetuximab, xelox)
Melanoma	WO 2013/059740 A1	Chemotherapeutics (e.g. aldesleukin, dabrafenib, dacarbazine, interferon alfa-2b, ipilimumab, peginterferon alfa-2b, trametinib, vemurafenib)

[00529]

[00530] (B) Cancers wherein the dysregulation of TrkA comprises one or more deletions, insertions or mutations in the TrkA protein, including:

Cancer	Literature reference(s)	Standard of care
Acute Myeloid leukemia	Meyer 2007: Leukemia 21: 2171–2180 Reuther et al. 2000: Mol Cell Biol 20:8655-8666	Chemotherapeutics as single agents (e.g. arsenic trioxide, cyclophosphamide, cytarabine, daunorubicin, doxorubicin, vincristine) or combinations (e.g. ADE)
Large Cell Neuroendocrine Carcinoma	Marchetti et al 2008: Human Mutation 29(5): 609-616	Radiotherapy (e.g. radioiodide therapy, external-beam radiation, radium 223 therapy) and/or chemotherapeutics (e.g. cisplatin, carboplatin, etoposide)
Neuroblastoma	Taconelli et al 2004: Cancer Cell 6: 347	Chemotherapeutics (e.g. cyclophosphamide, doxorubicin, vincristine)

[00531]

[00532] (C) Cancers driven by overexpression of wild-type TrkA (autocrine activation), including:

Cancer	Literature Reference(s)	Standard of care
Prostate Carcinoma	Walch et al: Clinical & Experimental Metastasis 17: 307–314 Papatsoris et al 2007: Expert Opinion on Investigational Drugs 16(3): 303-309	Radiotherapy (e.g. radium 223 therapy) or chemotherapeutics (e.g. abiraterone, cabazitaxel, degarelix, denosumab, docetaxel, enzalutamide, leuprolide, prednisone, sipuleucel-T)
Neuroblastoma	Van Noesel et al 2004: Gene 325: 1-15	Chemotherapeutics (e.g. cyclophosphamide, doxorubicin, vincristine)
Pancreatic Carcinoma	Zhang et al 2005: Oncology Reports 14: 161-171	Chemotherapeutics as single agents (e.g. erlotinib, fluorouracil, gemcitabine, mitomycin C) or combinations (e.g. gemcitabine-oxaliplatin)
Melanoma	Truzzi et al 2008: Journal of Investigative Dermatology 128(8): 2031	Chemotherapeutics (e.g. aldesleukin, dabrafenib, dacarbazine, interferon alfa-2b, ipilimumab, peginterferon alfa-2b, trametinib, vemurafenib)
Head and Neck Squamous Cell Carcinoma	Kolokythas et al 2010: Journal of Oral and Maxillofacial Surgery 68(6):1290-1295	Radiotherapy and/or chemotherapeutics (e.g. bleomycin, cetuximab, cisplatin, docetaxel, fluorouracil, methotrexate)
Gastric Carcinoma	Ni et al 2012: Asian Pacific Journal of Cancer Prevention 13: 1511	Chemotherapeutics (e.g. docetaxel, doxorubicin, fluorouracil, mitomycin C, trastuzumab)

[00533] In one embodiment, provided herein is a method for treating a patient diagnosed with a cancer having a dysregulation of TrkA, comprising administering to the patient a

therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, wherein the cancer is selected from non-small cell lung cancer, papillary thyroid carcinoma, glioblastoma multiforme, acute myeloid leukemia, colorectal carcinoma, large cell neuroendocrine carcinoma, prostate cancer, neuroblastoma, pancreatic carcinoma, melanoma, head and neck squamous cell carcinoma and gastric carcinoma.

[00534] In one embodiment, the compounds of the present invention are useful for treating cancer in combination with one or more additional therapeutic agents or therapies that work by the same or a different mechanism of action.

[00535] In one embodiment, the additional therapeutic agent(s) is selected from receptor tyrosine kinase-targeted therapeutic agents, including cabozantinib, crizotinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, pertuzumab, regorafenib, sunitinib, and trastuzumab.

[00536] In one embodiment, the additional therapeutic agent(s) is selected from signal transduction pathway inhibitors, including Ras-Raf-MEK-ERK pathway inhibitors (e.g. sorafenib, trametinib, vemurafenib), PI3K-Akt-mTOR-S6K pathway inhibitors (e.g. everolimus, rapamycin, perifosine, temsirolimus) and modulators of the apoptosis pathway (e.g. obataclax).

[00537] In one embodiment, the additional therapeutic agent(s) is selected from cytotoxic chemotherapeutics, including arsenic trioxide, bleomycin, cabazitaxel, capecitabine, carboplatin, cisplatin, cyclophosphamide, cytarabine, dacarbazine, daunorubicin, docetaxel, doxorubicin, etoposide, fluorouracil, gemcitabine, irinotecan, lomustine, methotrexate, mitomycin C, oxaliplatin, paclitaxel, pemetrexed, temozolomide, and vincristine.

[00538] In one embodiment, the additional therapeutic agent(s) is selected from angiogenesis-targeted therapies, including aflibercept and bevacizumab.

[00539] In one embodiment, the additional therapeutic agent(s) is selected from immune-targeted agents, including aldesleukin, ipilimumab, lambrolizumab, nivolumab, sipuleucel-T.

[00540] In one embodiment, the additional therapeutic agent(s) is selected from agents active against the TrkA pathway, including NGF-targeted biopharmaceuticals such as NGF antibodies, and panTrk inhibitors.

[00541] In one embodiment, the additional therapeutic agent or therapy is radiotherapy, including radioiodide therapy, external-beam radiation and radium 223 therapy.

[00542] In one embodiment, the additional therapeutic agent(s) includes any one of the above listed therapies or therapeutic agents which are standards of care in cancers wherein the cancer has a dysregulation of TrkA.

[00543] In one embodiment, provided herein is a method of treating cancer in a patient, comprising administering to said patient a compound of the invention or a pharmaceutically acceptable salt thereof, in combination with at least one additional therapy or therapeutic agent selected from radiotherapy (e.g. radioiodide therapy, external-beam radiation, radium 223 therapy), cytotoxic chemotherapeutics (e.g. arsenic trioxide, bleomycin, cabazitaxel, capecitabine, carboplatin, cisplatin, cyclophosphamide, cytarabine, dacarbazine, daunorubicin, docetaxel, doxorubicin, etoposide, fluorouracil, gemcitabine, irinotecan, lomustine, methotrexate, mitomycin C, oxaliplatin, paclitaxel, pemetrexed, temozolomide, vincristine), tyrosine kinase targeted-therapeutics (e.g. afatinib, cabozantinib, cetuximab, crizotinib, dabrafenib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, panitumumab, pertuzumab, regorafenib, sunitinib, trastuzumab), apoptosis modulators and signal transduction inhibitors (e.g. everolimus, perifosine, rapamycin, sorafenib, temsirolimus, trametinib, vemurafenib), immune-targeted therapies (e.g. aldesleukin, interferon alfa-2b, ipilimumab, lambrolizumab, nivolumab, prednisone, sipuleucel-T) and angiogenesis-targeted therapies (e.g. aflibercept, bevacizumab), wherein the amount of the compound of the invention or a pharmaceutically acceptable salt thereof is, in combination with the additional therapy or therapeutic agent, is effective in treating said cancer. These additional therapeutic agents may be administered with one or more compounds of the invention as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice known to one skilled in the art.

[00544] Also provided herein is (i) a pharmaceutical combination for treating cancer in a patient in need thereof, which comprises (a) a compound of the invention or a pharmaceutically acceptable salt thereof, (b) an additional therapeutic agent and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of a tumor disease, wherein the amounts of the compound or salt thereof and of the additional therapeutic agent are together effective in treating said cancer; (ii) a pharmaceutical composition comprising such a combination; (iii) the use of such a combination for the preparation of a medicament for the treatment of cancer; and (iv) a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and to a method of treatment of cancer a patient in need thereof.

[00545] In one embodiment, the combination therapy is for treating a cancer is selected from non-small cell lung cancer, papillary thyroid carcinoma, glioblastoma multiforme, acute myeloid leukemia, colorectal carcinoma, large cell neuroendocrine carcinoma, prostate cancer,

neuroblastoma, pancreatic carcinoma, melanoma, head and neck squamous cell carcinoma and gastric carcinoma.

[00546] Another embodiment of this invention provides a method of treating inflammation or an inflammatory disease or disorder in a mammal, comprising administering to said mammal in need thereof one or more compounds of Formula I or a pharmaceutically acceptable salt thereof in an amount effective to treat said inflammation. In one embodiment, the inflammatory disease is inflammatory lung diseases (such as asthma), interstitial cystitis, bladder pain syndrome, inflammatory bowel diseases (including ulcerative colitis and Crohn's disease), and inflammatory skin diseases such as atopic dermatitis.

[00547] In one embodiment, the method of treating inflammation or an inflammatory disease or disorder comprises administering a compound of the invention in combination with one or more additional agents. Examples of additional agents include anti-TNF treatments (for example monoclonal antibody such as infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), and golimumab (Simponi), or a circulating receptor fusion protein such as etanercept (Enbrel)), antimetabolite and antifolate drug (for example Methotrexate), or targeted kinase inhibitors (for example JAK family inhibitors Ruxolitinib, Tofacitinib, CYT387, Lestaurtinib, Pacritinib and TG101348).

[00548] Another embodiment of this invention provides a method of treating Trypanosoma cruzi infection in a mammal, comprising administering to said mammal in need thereof one or more compounds of Formula I or a pharmaceutically acceptable salt thereof in an amount effective to treat said Trypanosoma cruzi infection.

[00549] Another embodiment of this invention provides a method of treating Sjogren's syndrome in a mammal, comprising administering to said mammal in need thereof one or more compounds of Formula I or a pharmaceutically acceptable salt thereof in an amount effective to treat said syndrome.

[00550] Another embodiment of this invention provides a method of treating endometriosis in a mammal, comprising administering to said mammal in need thereof one or more compounds of Formula I or a pharmaceutically acceptable salt thereof in an amount effective to treat said endometriosis.

[00551] Another embodiment of this invention provides a method of treating diabetic peripheral neuropathy in a mammal, comprising administering to said mammal in need thereof one or more compounds of Formula I or a pharmaceutically acceptable salt thereof in an amount effective to treat said diabetic peripheral neuropathy.

[00552] Another embodiment of this invention provides a method of treating prostatitis in a mammal, comprising administering to said mammal in need thereof one or more compounds of Formula I or a pharmaceutically acceptable salt thereof in an amount effective to treat said prostatitis.

[00553] Another embodiment of this invention provides a method of treating pelvic pain syndrome in a mammal, comprising administering to said mammal in need thereof one or more compounds of Formula I or a pharmaceutically acceptable salt thereof in an amount effective to treat said pelvic pain syndrome.

[00554] Another embodiment of this invention provides a method of treating a neurodegenerative disease in a mammal, comprising administering to said mammal in need thereof one or more compounds of Formula I or a pharmaceutically acceptable salt thereof in an amount effective to treat said neurodegenerative disease.

[00555] As used herein, an "effective amount" means an amount of compound that, when administered to a mammal in need of such treatment, is sufficient to (i) treat a particular disease, condition, or disorder which can be treated with a compound of Formula I, or (ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, condition, or disorder described herein.

[00556] The amount of a compound of Formula I that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the mammal in need of treatment, but can nevertheless be routinely determined by one skilled in the art.

[00557] As used herein, the term "mammal" refers to a warm-blooded animal that has or is at risk of developing a disease described herein and includes, but is not limited to, guinea pigs, dogs, cats, rats, mice, hamsters, and primates, including humans.

[00558] The compounds of the present invention can be used in combination with one or more additional therapeutic agents that work by the same or a different mechanism of action. Examples of additional therapeutic agents include anti-inflammatory compounds, steroids (e.g., dexamethasone, cortisone and fluticasone), analgesics such as NSAIDs (e.g., aspirin, ibuprofen, indomethacin, and ketoprofen), and opioids (such as morphine), and chemotherapeutic agents.

[00559] Also provided herein is a pharmaceutical combination comprising an effective amount of: (a) at least one compound of Formula I; and (b) at least one additional therapeutic agent selected from anti-inflammatory compounds, steroids (e.g., dexamethasone, cortisone and fluticasone), analgesics such as NSAIDs (e.g., aspirin, ibuprofen, indomethacin, and

ketoprofen), and opioids (such as morphine), for use in the treatment of pain in a mammal, wherein (a) and (b) can be in separate dosage forms or in the same dosage form.

[00560] The term "pharmaceutical combination" as used herein refers to a pharmaceutical therapy resulting from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that at least one of the compounds of Formula I, and at least one additional therapeutic agent are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that at least one of the compounds of Formula I, and at least one additional therapeutic agent, are administered to a patient as separate entities either simultaneously or sequentially with variable intervening time limits, wherein such administration provides effective levels of the two or more compounds in the body of the patient. These also apply to cocktail therapies, e.g. the administration of three or more active ingredients.

[00561] Also provided herein is a method of treating pain in a mammal, comprising co-administering to a mammal in need thereof an effective amount of: (a) at least one compound of Formula I; and (b) at least one additional therapeutic agent selected from anti-inflammatory compounds, steroids (e.g., dexamethasone, cortisone and fluticasone), analgesics such as NSAIDs (e.g., aspirin, ibuprofen, indomethacin, and ketoprofen), opioids (such as morphine), calcitonin gene-related peptide receptor antagonists, subtype-selective ion channel modulators, anticonvulsants (for example Pregabalin and gabapentin), dual serotonin-norepinephrin reuptake inhibitors (for example duloxetine, venlafaxine and milnacipran), and tricyclic antidepressants (such as amitriptyline, nortriptyline and desipramine).

[00562] Another embodiment of this invention provides a method of treating diseases related to an imbalance of the regulation of bone remodeling in a mammal, comprising administering to said mammal in need thereof one or more compounds of Formula I or a pharmaceutically acceptable salt thereof in an amount effective to treat said disease. In one embodiment, the disease is osteoporosis, rheumatoid arthritis, and bone metastases.

[00563] In one embodiment, the method for treating diseases related to an imbalance of the regulation of bone remodeling in a mammal comprises administering a TrkA inhibitor of the invention in combination with one or more additional therapeutic agents or therapies. Examples of additional therapeutic agents or therapies include anti-TNF treatments (for example monoclonal antibody such as infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), and golimumab (Simponi), or with a circulating receptor fusion protein such as etanercept (Enbrel)), antimetabolite and antifolate drug (for example Methotrexate), or targeted

kinase inhibitors (for example JAK family inhibitors Ruxolitinib, Tofacitinib, CYT387, Lestaurtinib, Pacritinib and TG101348).

[00564] The term "co-administering" is meant to encompass administration of the selected therapeutic agents to a single patient, and is intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different times. This term encompasses administration of two or more agents to a mammal so that both agents and/or their metabolites are present in the mammal at the same time. It includes simultaneous administration in separate compositions, administration at different times in separate compositions, and/or administration in a composition in which both agents are present. In some embodiments, the compound(s) of the invention and the other therapeutic agent(s) are administered in a single composition. In some embodiments, compound(s) of the invention and the other agent(s) are admixed in the composition.

[00565] Also provided herein is a medicament containing a compound of Formula I for treatment of pain in a mammal in combination with an additional therapeutic agent selected from anti-inflammatory compounds, steroids (e.g., dexamethasone, cortisone and fluticasone), analgesics such as NSAIDs (e.g., aspirin, ibuprofen, indomethacin, and ketoprofen), and opioids (such as morphine).

[00566] Also provided herein is a medicament containing a therapeutic agent selected from anti-inflammatory compounds, steroids (e.g., dexamethasone, cortisone and fluticasone), analgesics such as NSAIDs (e.g., aspirin, ibuprofen, indomethacin, and ketoprofen), and opioids (such as morphine) for treatment of pain in a mammal in combination with a compound of Formula I.

[00567] Compounds of the invention may be administered by any convenient route, e.g. into the gastrointestinal tract (e.g. rectally or orally), the nose, lungs, musculature or vasculature, or transdermally or dermally. Compounds may be administered in any convenient administrative form, e.g. tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g. diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents. If parenteral administration is desired, the compositions will be sterile and in a solution or suspension form suitable for injection or infusion. Such compositions form a further aspect of the invention.

[00568] Another formulation may be prepared by mixing a compound described herein and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage

Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (*i.e.*, a compound described herein or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (*i.e.*, medicament).

[00569] Accordingly, another aspect of the present invention provides a pharmaceutical composition, which comprises a compound of Formula I or a pharmaceutically acceptable salt thereof, as defined hereinabove, together with a pharmaceutically acceptable diluent or carrier.

[00570] According to another embodiment, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of pain in a mammal. In one embodiment, the pain is chronic pain. In one embodiment the pain is acute pain. In one embodiment, the pain is inflammatory pain, neuropathic pain, or pain associated with cancer, surgery, or bone fracture.

[00571] According to another embodiment, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a mammal.

[00572] In another embodiment, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of inflammation or an inflammatory disease or disorder in a mammal. In one embodiment, the inflammatory disease is inflammatory lung diseases (such as asthma), interstitial cystitis, bladder pain syndrome, inflammatory bowel diseases (including ulcerative colitis and Crohn's disease), and inflammatory skin diseases such as atopic dermatitis.

[00573] In another embodiment, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of infectious diseases, for example *Trypanosoma cruzi* infection, in a mammal.

[00574] In another embodiment, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of Sjogren's syndrome in a mammal.

[00575] In another embodiment, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of endometriosis in a mammal.

[00576] In another embodiment, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of diabetic peripheral neuropathy in a mammal,

[00577] In another embodiment, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of prostatitis in a mammal,

[00578] In another embodiment, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of pelvic pain syndrome in a mammal,

[00579] In another embodiment, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of a neurodegenerative disease in a mammal.

[00580] According to a further aspect, the present invention provides the use of a compound of Formula I or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition selected from pain, cancer, inflammation, neurodegenerative disease or *Trypanosoma cruzi* infection. In one embodiment, the condition is chronic pain. In one embodiment, the condition is acute pain. In one embodiment, the pain is inflammatory pain, neuropathic pain, or pain associated with cancer, surgery, or bone fracture. In one embodiment, the condition is cancer. In one embodiment, the condition is inflammation. In one embodiment, the condition is a neurodegenerative disease. In one embodiment, the condition is *Trypanosoma cruzi* infection. In one embodiment, the condition is Sjogren's syndrome. In one embodiment, the condition is endometriosis. In one embodiment, the condition is diabetic peripheral neuropathy. In one embodiment, the condition is prostatitis. In one embodiment, the condition is pelvic pain syndrome.

Examples

[00581] The following examples illustrate the invention. In the examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company, Lancaster, TCI or Maybridge, and were used without further purification unless otherwise indicated. THF, DCM, toluene, DMF and dioxane were purchased from Aldrich in Sure/Seal™ bottles and used as received.

[00582] The reactions set forth below were done generally under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried.

[00583] Column chromatography was done on a Biotage system (Manufacturer: Dyax Corporation) having a silica gel or C-18 reverse phase column, or on a silica SepPak cartridge (Waters).

Biological assays

Example A-1

TrkA Kinase Binding Assay

[00584] TrkA binding activity was determined in a TrkA LanthaScreen™ Eu Kinase Binding Assay. 5 nM His-tagged recombinant human TrkA (6HIS tagged cytoplasmic domain from Invitrogen, Catalog No. PV3144) was incubated with 4 nM Alexa-Fluor® Tracer 236 (Invitrogen Cat. No. PV5592), 2 nM biotinylated anti-His (Invitrogen Cat. No. PV6090), and 2 nM europium-labeled Streptavidin (Invitrogen Cat. No. PV5899), in buffer (25 mM MOPS, pH 7.5, 5 mM MgCl₂, 0.005% Triton X-100). Three fold serial dilutions of compounds of the invention in DMSO were added to a final percentage of 2% DMSO. After 60-minute incubation at 22 °C, the reaction was measured using the EnVision mutlimode plate reader (PerkinElmer) via TR-FRET dual wavelength detection at 615 nM and 665 nM. The percent of control was calculated using a ratiometric emission factor. The IC₅₀ values were determined by fitting a four parameter model to the percent of control data.

[00585] Table A provides averaged IC₅₀ values for compounds of the invention when tested in the assay of Example A, where **A** represents an averaged IC₅₀ value <100 nM; **B** represents an averaged IC₅₀ value from 100 to 1,000 nM, and **C** represents an averaged IC₅₀ value between >1,000 nM and 3,000 nM.

Table A

Ex. #	TrkA Enzyme IC₅₀ (nM)
1	A
2	A
3	A
4	B
5	B
6	A
7	B
8	B
9	B
10	A
11	A
12	A
13	B
14	B
15	A
16	A
17	B
18	B
19	B
20	B
21	B
22	B
23	B
24	B
25	A
26	A
27	A

Ex. #	TrkA Enzyme IC₅₀ (nM)
28	A
29	A
30	A
31	A
32	A
33	A
34	A
35A	A
35B	B
36	B
37	B
38	B
39	A
40	B
41	A
42	A
43	B
44	A
45	A
46	A
47	B
48	B
49	B
50	B
51	B
52	B
53	B
54	B
55	A
56	A

Ex. #	TrkA Enzyme IC ₅₀ (nM)
57	A
58	A
59	A
60	A
61	A
62	A
63	A
64	A
65	A
66	A
67	A
68	A
69	A
70	A
71	A
72	A
73	A
74	A
75	A
76	A
77	A
78	A
79	A
80	A
81	A
82	A
83	A
84	A
85	A
86	A

Ex. #	TrkA Enzyme IC₅₀ (nM)
87	A
88	A
89	A
90	A
91	A
92	A
93	A
94	A
95	A
96	A
97	A
98	C
99	A
100	A
101	A
102	A
103	A
104	A
105	A
106	A
107	A
108	A
109	A
110	A
111	A
112	A
113	B
114	A
115	A
116	A

Ex. #	TrkA Enzyme IC₅₀ (nM)
117	A
118	A
119	A
120	A
121	A
122	A
123	A
124	A
125	A
126	B
127	B
128	B
129	A
130	A
131	A
132	A
133	A
134	A
135	C
136	A
137	A
138	B
139	A
140	A
141	A
142	A
143	A
144	A
145	B
146	A

Ex. #	TrkA Enzyme IC ₅₀ (nM)
147	A
148	A
149	A
150	A
151	A
152	A
153	A
154	A
155	A
156	A
157	A
158	A
159	A
160	A

p38 α Kinase Binding Assay

[00586] p38 α binding activity was determined in a p38 α LanthaScreen™ Eu Kinase Binding Assay. 5 nM of inactive, GST-tagged recombinant human p38 α (GST-tagged cytoplasmic domain from Invitrogen, Catalog No. PV3305) was incubated with 5 nM Alexa-Fluor® Tracer 199 (Invitrogen Cat. No. PV5830), and 2 nM europium labeled anti-GST antibody (Invitrogen Cat. No. PV5594), in buffer (25 mM [Na⁺] HEPES pH 7.3, 10 mM MgCl₂, 100 μ M NaVO₄). Three fold serial dilutions of compounds of the invention in DMSO were added to a final percentage of 2% DMSO. After 60-minute incubation at 22 °C, the reaction was measured using the EnVision multimode plate reader (PerkinElmer) via TR-FRET dual wavelength detection at 615 nM and 665 nM. The percent of control was calculated using a ratiometric emission factor. The IC₅₀ values were determined by fitting a four parameter model to the percent of control data. The compounds of Examples 1-160 were tested in this assay, and all compounds were found to be about 1000 fold more potent against TrkA than p38 α .

Example B

Off-Target Kinase Profiling

[00587] Representative compounds (Examples 12, 32, 26 and 2) of the invention were

tested for off-target kinase activity at a concentration of 10 μ M by Millipore, Inc. in their KinaseProfiler™ service against all the kinases available in their full kinase panel. Compounds were run in duplicate at a concentration of ATP near the K_m for each individual kinase according to Millipore's specifications. The results are shown in Table B. Data are reported as percent of control (POC) and are the average of the two replicates.

[00588] In the KinaseProfiler™ the representative compounds showed remarkable and unexpected selectivity for inhibiting TrkA and TrkB versus other kinases in the panel. In fact, the compounds were largely inactive against off-target kinases at a concentration of 10 μ M, and thus would not be expected to inhibit off-target kinases at therapeutic doses in mammals. The ability of compounds of the invention to selectively inhibit the Trk pathway without inhibiting other off-target kinases could translate into drug profiles that are essentially free of side-effects related to inhibition of off-target kinases. Such a drug profile would represent a safer approach to treating pain, inflammation, cancer and certain skin diseases than has been previously reported.

Table B

Kinase	Example 12 Avg. POC	Example 32 Avg. POC	Example 26 Avg. POC	Example 2 Avg. POC
Abl2	118	121.5	105	112.5
Abl-P	135.5	124.5	131	146.5
AKT1	105.5	92	100	130.5
AKT2	127	121	130	132
AKT3	94	77.5	96	116.5
ALK	103	127	117	111
ALK4	101	100.5	102.5	98.5
AMPK(A1/B1/G1)	117	138.5	122.5	152.5
ARK5	99.5	118.5	100.5	109.5
AURKA	111	112.5	107.5	126
Axl	106	119.5	107	113.5
BLK_m	112	111	103.5	126
Bmx	115.5	106.5	109.5	113
BrSK1	111.5	114.5	105.5	119
BrSK2	147	128.5	118	139.5
BTK	127	119	139	111.5
CAMK1	102	100	106	109.5
CAMK1d	137	114	97	127
CAMK2b	106	102.5	107	106.5
CAMK2d	110.5	108.5	99.5	119
CAMK2g	107.5	105	101	107.5
CAMK4	113.5	102	121	137.5
CDK1/cyclinB	107.5	104	103	122.5
CDK2/cyclinA	112	118	114.5	127
CDK2/cyclinE	96.5	106	97.5	116.5
CDK3/cyclinE	98.5	102.5	101.5	105.5

Kinase	Example 12 Avg. POC	Example 32 Avg. POC	Example 26 Avg. POC	Example 2 Avg. POC
CDK5/p25	104	106	109	107.5
CDK5/p35	106.5	112	110.5	124
CDK6/cyclinD3	103	108	104.5	100
CDK7/cyclinH/MAT1	101	122.5	113.5	111
CDK9/cyclinT1	106	106.5	112.5	127
CHK1	99.5	103	70.5	106.5
CHK2	92	112	109	119
CK1 _γ	101	107.5	104.5	100.5
CK1 δ	109.5	135.5	121.5	117.5
CK1 γ 1	98.5	111.5	106.5	116.5
CK1 γ 2	114.5	101.5	112.5	142.5
CK1 γ 3	104.5	102	102.5	118
CK2	98	97	110.5	107
CK2 α 2	107.5	104	114	125
CLK2	100	105.5	108.5	115.5
CLK3	100	109	106	108
c-RAF	96	101.5	106.5	103.5
CSK	131.5	123	118.5	124
DAPK1	136	131	135	108.5
DAPK2	102.5	103	108.5	123.5
DAPK3	103	111	103	125.5
DCAMKL2	169	146	135	157.5
DDR2	107	116	111	113
DMPK	104	98.5	106	105
DRAK1	114	105.5	125	108.5
DYRK2	97.5	97.5	103	98
eEF-2K	140	115	127.5	138
EGFR	109.5	102	108	114
EphA1	100	114	101	85
EphA2	113	118	102	129
EphA3	114.5	122	128	123.5
EphA4	114.5	103	110	111.5
EphA5	118.5	104.5	106.5	119
EphA7	96.5	100.5	108	116
EphA8	122.5	109	118.5	128.5
EphB1	114	145.5	116.5	108.5
EphB2	112	96.5	109.5	125
EphB3	89	87.5	97	110
EphB4	121	106	115	118.5
ErbB4	122	108.5	115.5	148
ERK1	105	107	109.5	120.5
ERK2	106.5	128.5	107.5	112.5
FAK	104	116.5	105	116.5
FAK2	111	101.5	104.5	120
Fer	100.5	85	98	110.5
Fes	110	112.5	100.5	129.5
FGFR1	90	104.5	104.5	114

Kinase	Example 12 Avg. POC	Example 32 Avg. POC	Example 26 Avg. POC	Example 2 Avg. POC
FGFR2	114	110.5	112	112.5
FGFR3	109	107	101	113.5
FGFR4	119	139.5	123	124
Fgr	114.5	109.5	114.5	131
Flt1	93	103	104	105.5
Flt3	90	115	97.5	96.5
Flt4	83.5	98	106	99
Fms	91	102	96	82
Fyn	92.5	111	115.5	123.5
GRK5	83.5	90	86	106.5
GRK6	103	101	100.5	103.5
GRK7	117	117.5	118	108.5
GSK3alpha	119.5	112.5	115.5	123.5
GSK3beta	109.5	84.5	124.5	126
Haspin	97	94	92	92.5
Hck	103.5	98	91.5	85.5
HIPK1	102.5	115	111	97
HIPK2	91.5	99.5	103	97
HIPK3	102.5	107	111	119.5
IGF-1R	80	84.5	60.5	18
IGF-1R Activated	102.5	112.5	98	95
IKKalpha	119.5	102	112.5	141.5
IKKbeta	102	105.5	103.5	116
IR	92	109	82.5	44
IR Activated	109	111.5	106	103
IRAK1	102.5	113.5	110.5	107
IRAK4	95.5	99	102	125.5
IRR	91	109.5	89	2.5
ITK	114.5	124	122	117.5
JAK2	122.5	122.5	134.5	233
JAK3	112	109.5	112	142.5
JNK1alpha1	109.5	118	112	94
JNK2alpha2	96	102.5	104	103.5
JNK3	107.5	104	116	117.5
KDR	119.5	129	144.5	123.5
KIT	102.5	94.5	94	104
Lck	92	104.5	96.5	97.5
LIMK1	97.5	95	102	105
LKB1	91	100	95	103.5
LOK	116	103.5	109	109.5
Lyn	104.5	106.5	110.5	115
MAP3K5	111	116	116.5	105
MAP4K2	107.5	119.5	121	110
MAPKAP-K2	122.5	117.5	120	137.5
MAPKAP-K3	112	105	108.5	128
MAPKAP-K5	96	108	101.5	113.5
MARK1	104	98.5	98.5	103

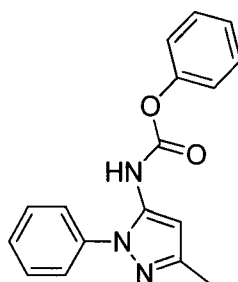
Kinase	Example 12 Avg. POC	Example 32 Avg. POC	Example 26 Avg. POC	Example 2 Avg. POC
MARK2	105.5	107.5	102.5	109
MEK1	106.5	102	97	100.5
MELK	67	98	86	142
Mer	98	104	98	109.5
Met	109	118.5	81	148.5
MINK	102	124	126.5	110.5
MKK4_m	144.5	133	99.5	102.5
MKK6	123	134.5	121.5	130
MKK7beta	122.5	138.5	144.5	129.5
MKNK2	103.5	99.5	99.5	106.5
MLK1	103.5	104.5	105.5	75
MRCKalpha	139	131	124.5	127.5
MRCKbeta	103.5	103	110	129.5
MSK1	127.5	118	114	113.5
MSK2	127	99.5	107.5	112
MSSK1	112.5	105.5	120.5	116
MST1	92	105.5	102	111.5
MST2	106.5	111.5	111	110.5
MST3	131.5	130.5	108.5	120
mTOR	104.5	94.5	102.5	116
mTOR/FKBP12	105.5	113.5	107.5	105
MuSK	98.5	104.5	99.5	103.5
MYLK	99	97.5	101	100
NEK11	84.5	108	113.5	108.5
NEK2	91.5	108	100.5	104
NEK3	102	113	105	105
NEK6	121	123	123.5	125.5
NEK7	133.5	122.5	126	94.5
NLK	115.5	125.5	100.5	111
p38alpha	110	96.5	104.5	102.5
p38beta	115.5	119	115.5	113
p38delta	99.5	113.5	102	96.5
p38gamma	111	116.5	118	115
p70S6K	124.5	110.5	116	172
PAK2	97	108.5	99.5	104
PAK4	103	98	100.5	95
PAK5	143	111	121.5	109.5
PAK6	139	116.5	116.5	119.5
PASK	125.5	137	124.5	143
PDGFRalpha	104.5	112.5	104.5	123
PDGFRbeta	125.5	131.5	122.5	149
PDK1	105.5	101.5	115	120.5
PhKgamma2	110	102.5	108.5	113
Pim-1	106	109	97.5	173
Pim-2	118.5	116.5	120.5	148
Pim-3	100.5	112	98	98
PKAC-alpha	120.5	90	116	138.5

Kinase	Example 12 Avg. POC	Example 32 Avg. POC	Example 26 Avg. POC	Example 2 Avg. POC
PKCalpha	104	110	107.5	96
PKCbetaI	93.5	80	89	99
PKCbetaII	100	100.5	99	95.5
PKCdelta	97.5	99	105	95
PKCepsilon	97.5	97.5	106.5	101.5
PKCeta	100	111.5	98	107
PKCgamma	104.5	104	99	102
PKCiota	69.5	71	85.5	95.5
PKCtheta	117.5	117	109	101
PKCzeta	99.5	115	108.5	122.5
PKD1	115	98.5	113.5	110.5
PKD2	94	110.5	102	102
Plk1	98.5	108	108	95
Plk2	103.5	103	101.5	102
Plk3	115	103.5	119	103
PRK2	97.5	99.5	110.5	128
PRKG1alpha	89.5	84	98	127.5
PRKG1beta	95.5	80.5	111.5	122
PrKX	118.5	110	109	152
PTK5	100	104	110	122
PTK6	125.5	100	121	129
Ret	85	100.5	106.5	118.5
RIPK2	99	99.5	98	108
ROCK-I	116.5	103	112	116.5
ROCK-II	99	106	110	108
Ron	116.5	107	101	106.5
Ros	97.5	97.5	106.5	106.5
Rse	106	105	109.5	109
Rsk1	107.5	111.5	121	117
Rsk2	103	92.5	105.5	137
Rsk3	90	92	76.5	106
Rsk4	101	95	99.5	140
SGK1	129	119	97.5	150
SGK2	148	123.5	123.5	166.5
SGK3	143.5	134	104	137.5
SIK	133.5	97	121.5	121.5
SRC	97	108.5	104.5	99.5
SRPK1	97.5	99.5	102.5	122
SRPK2	101.5	106.5	106	106
STK33	106.5	115	111	110.5
Syk	108.5	115	93.5	115
TAK1	97	99.5	108.5	106
TAO1	104	100	105.5	110.5
TAO2	121	104	111	110
TAO3	99	105	109	111
TBK1	103	108.5	113	116
TEC Activated	122.5	108.5	113.5	153

Kinase	Example 12 Avg. POC	Example 32 Avg. POC	Example 26 Avg. POC	Example 2 Avg. POC
Tie2	104.5	121	106.5	126
TLK2	98	92	97	100
TNK2	117.5	132	123	100.5
TrkA	-0.5	0	0.5	1.5
TrkB	1	-0.5	1.5	-2
TSSK1	79	88.5	71.5	106
TSSK2	139	120.5	128	118.5
Txk	139	127	119	125
ULK2	99	103	102	99
ULK3	89.5	92	92.5	105
VRK2	95	100.5	98	109
WNK2	106.5	108.5	108	99
WNK3	112.5	103.5	103.5	109.5
Yes	119.5	114.5	117.5	132.5
ZAP-70	140	124	120.5	124

Preparation of Synthetic Intermediates

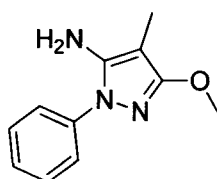
Intermediate 1



Preparation of phenyl (3-methyl-1-phenyl-1H-pyrazol-5-yl)carbamate

[00589] To a solution of 3-methyl-1-phenyl-1H-pyrazol-5-amine (500 mg, 2.887 mmol) in EtOAc (25 mL) was added aqueous sodium hydroxide (2 M) (4.33 mL, 8.660 mmol) followed by phenyl carbonochloridate (0.54 mL, 4.33 mmol). The reaction was stirred at ambient temperature overnight, diluted with EtOAc (10 mL) and the phases were separated. The organic phase was washed with H₂O (10 mL), brine (10 mL), dried (MgSO₄), filtered and concentrated to a pale yellow solid. The crude product was triturated with hexanes (20 mL) and filtered, yielding pure product as off-white solid. MS (apci) m/z = 294.1 (M+H).

Intermediate 2

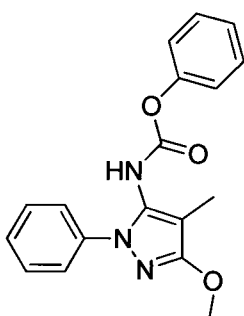


3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-amine

[00590] Step A: Preparation of 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one: A mixture of ethyl 2-cyanopropanoate (5.0 g, 46 mmol) and phenylhydrazine (5.9 g, 46 mmol) in dioxane (10 mL) was heated at 110 °C for 17 hours. The mixture was cooled to ambient temperature and concentrated. The residual solid was triturated with cold EtOH and suspended in Et₂O. The solid was filtered, washed with Et₂O and dried under vacuum to give the product as a white solid (3.4 g, 39% yield). MS (apci) m/z = 190.0 (M-H).

[00591] Step B: Preparation of 3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-amine: To a fine suspension of 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one (300 mg, 1.59 mmol) in 1:1 CH₂Cl₂-MeOH (6.0 mL) was added 2M TMSCHN₂ in hexanes (951 µL, 1.90 mmol). The mixture was stirred at ambient temperature for 2 hours and additional 2M TMSCHN₂ in hexanes (1.0 mL) was added. The mixture was stirred for 2 hours and concentrated. The residual syrup was partitioned into H₂O and 50% EtOAc-hexanes and stirred for 15 minutes. The organic layer was removed and the aqueous layer was extracted with 50% EtOAc-hexanes (2X). The combined organic fractions were washed with saturated NaCl and dried over MgSO₄/activated carbon. The dried solution was eluted through a SiO₂ plug eluting with 50% EtOAc-hexanes. The eluent was concentrated to a colorless syrup that was dried under vacuum to afford the title compound as a white solid (153 mg, 47 % yield). ¹H NMR (CDCl₃) δ 7.52 (d, J=7.7 Hz, 2H), 7.42 (t, J=7.6 Hz, 2H), 7.24 (t, J=7.3 Hz, 1H), 3.94 (s, 3H), 3.59 (br s, 2H), 1.83 (s, 3H) ppm.

Intermediate 3

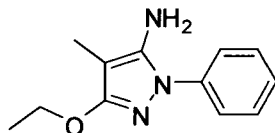


phenyl (3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)carbamate

[00592] A solution of 3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-amine (140 mg, 0.689 mmol) in EtOAc (3.0 mL) was cooled to 0 °C and 2M NaOH (689 µL, 1.38 mmol) and phenylchloroformate (129 µL, 1.03 mmol) were added sequentially. The mixture was stirred for 5 minutes, allowed to reach ambient temperature and stirred for 3 hours. The reaction mixture was diluted with hexanes (3 mL) and washed with H₂O (2x), 1M HCl, H₂O and saturated NaCl. The organic fraction was dried over MgSO₄/activated carbon and filtered through a SiO₂ plug eluting with 50 % EtOAc-hexanes. The eluent was concentrated, and the residual colorless syrup was dissolved in dry Et₂O and concentrated to a white foam. The foam was sonicated

under hexanes until a fine granular suspension formed. The solvent was decanted, the residual solid was washed with hexanes and dried under vacuum to afford the title compound as a white solid (185 mg, 83% yield). ^1H NMR (CDCl_3) δ 7.50-7.10 (m, 9H), 6.75 (br unresolved, 1H), 6.47 (s, 1H), 3.97 (s, 3H), 1.96 (s, 3H) ppm.

Intermediate 4

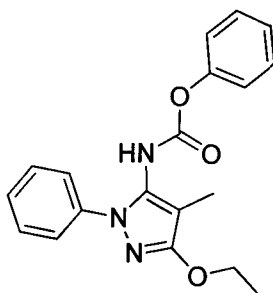


3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-amine

[00593] Step A: Preparation of 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one: A mixture of ethyl 2-cyanopropanoate (5.0 g, 46 mmol) and phenylhydrazine (5.9 g, 46 mmol) in dioxane (10 mL) was heated at 110 °C for 17 hours. The crude material was cooled to ambient temperature, concentrated, and triturated with cold EtOH and Et₂O. The resultant solid was filtered, washed with Et₂O, and dried under vacuum to give the product as a white solid (3.4 g, 39 % yield). MS (apci) m/z = 190.0 (M-H).

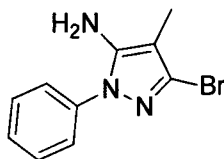
[00594] Step B: Preparation of 3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-amine: To a suspension of 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one (10.0 g, 52.9 mmol) in DMF (100 mL) was added K₂CO₃ (14.6 g, 106 mmol) and bromoethane (4.34 mL, 58.1) at ambient temperature. After stirring for 17 hours, the reaction mixture was treated with EtOAc and washed with water (3x) and brine, dried (MgSO₄), filtered, and concentrated to give the product (5.35 g, 47 % yield). MS (apci) m/z = 218.1 (M+H).

Intermediate 5

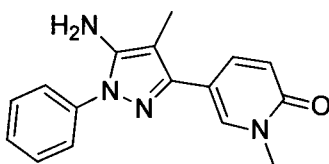


phenyl 3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-ylcarbamate

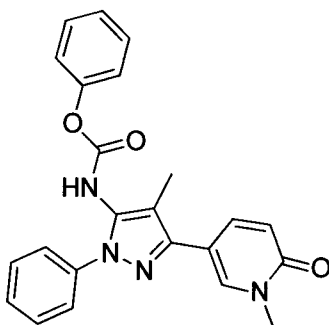
[00595] Prepared by the method as described for Intermediate 1 using 3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-amine instead of 3-methyl-1-phenyl-1H-pyrazol-5-amine. The material (4.43 g, 13.13 mmol, 99.8 % yield) was used without purification. MS (apci) m/z = 338.1 (M+H).

Intermediate 6**3-bromo-4-methyl-1-phenyl-1H-pyrazol-5-amine**

[00596] To a stirred solution of 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one (1.00 g, 5.29 mmol) in MeCN (20 mL) was added POBr₃ (2.27 g, 7.93 mmol). The reaction mixture was heated at reflux for 3 hours. The reaction was concentrated under vacuum. The residue was taken up in DCM. Saturated aqueous NaHCO₃ solution was carefully added. The aqueous layer was extracted with DCM. The combined organic extracts were washed with brine, dried and concentrated. The residue was purified by flash chromatography on silica gel (1:2 hexane/EtOAc to give the title compound (0.23 g, 17% yield). MS (apci) m/z = 252.0; 254.0 (M+H).

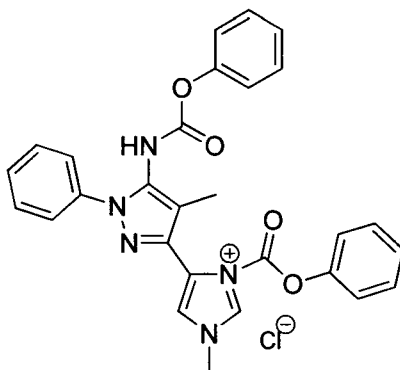
Intermediate 7**5-(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)-1-methylpyridin-2(1H)-one**

[00597] 3-bromo-4-methyl-1-phenyl-1H-pyrazol-5-amine (763 mg, 3.03 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)one (1.42 g, 6.05 mmol), K₂CO₃ (1.67 g, 12.1 mmol) and Pd(PPh₃)₄ (350 mg, 0.30 mmol) were combined in toluene (10 mL), water (5 mL) and EtOH (2.5 mL) and warmed to 95 °C in a sealed tube for 16 hours. The cooled mixture was filtered and the filtrate partitioned between water (30 mL) and EtOAc (30 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by silica column chromatography eluting with 2% MeOH/DCM to afford the title compound (504 mg, 59% yield) as a yellow foam. MS (apci) m/z = 281.2 (M+H).

Intermediate 8

phenyl (4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)carbamate

[00598] To a suspension of 5-(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)-1-methylpyridin-2(1H)-one (2.80 g, 9.99 mmol) in EtOAc (120 mL) was added 2N NaOH (14.98 mL, 29.97 mmol) followed by phenyl chloroformate (2.5 mL, 19.98 mmol). The mixture was stirred at ambient temperature for 16 hours then partitioned between water (100 mL) and EtOAc (100 mL) and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with saturated NaHCO₃ (50 mL) and brine (50 mL) then dried over Na₂SO₄, filtered and concentrated to afford the title compound as a pale yellow syrup which was used directly without purification, assuming 100% yield. MS (apci) m/z = 401.2 (M+H).

Intermediate 9

Preparation of 1-methyl-4-(4-methyl-5-(phenoxycarbonylamino)-1-phenyl-1H-pyrazol-3-yl)-3-(phenoxycarbonyl)-1H-imidazol-3-ium chloride

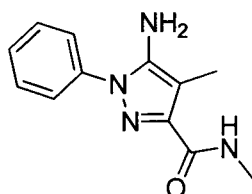
[00599] Step A: Preparation of 2-methyl-3-(1-methyl-1H-imidazol-4-yl)-3-oxopropanenitrile. Propiononitrile (0.893 g, 16.2 mmol) was added dropwise to a 1M solution of LHMDS (13.0 mL, 13.0 mmol) in THF at -78 °C. The mixture was stirred for 30 minutes and a solution of ethyl 1-methyl-1H-imidazole-4-carboxylate (1.00 g, 6.49 mmol) in THF (20 mL, heated to dissolve the starting material) was added dropwise. The reaction was allowed to warm to ambient temperature, stirred overnight, poured into ice water (50 mL) and extracted with EtOAc (100 mL). The pH was adjusted to 6.5 using 2N HCl and the mixture was extracted with EtOAc

(100 mL). The pH was then adjusted to 6 using 2N HCl and the mixture was extracted with EtOAc (2x 100 mL). The combined extracts from the pH 6.5 and pH 6 extractions were dried (MgSO_4), filtered and concentrated to provide the title compound (1.02 g, 6.25 mmol, 96.4 % yield). MS (apci) $m/z = 164.2$ (M+H).

[00600] Step B: Preparation of 4-methyl-3-(1-methyl-1H-imidazol-4-yl)-1-phenyl-1H-pyrazol-5-amine hydrochloride. A pressure vessel was charged with 2-methyl-3-(1-methyl-1H-imidazol-4-yl)-3-oxopropanenitrile (1.00 g, 6.13 mmol), absolute EtOH (12.3 mL, 6.13 mmol) and phenylhydrazine hydrochloride (0.975 g, 6.74 mmol). The reaction was sealed, heated at 80 °C overnight and concentrated to afford the title compound (1.70 g, 5.87 mmol, 95.7% yield). MS (apci) $m/z = 254.1$ (M+H).

[00601] Step C: Preparation of 1-methyl-4-(4-methyl-5-(phenoxycarbonylamino)-1-phenyl-1H-pyrazol-3-yl)-3-(phenoxycarbonyl)-1H-imidazol-3-ium chloride. 4-methyl-3-(1-methyl-1H-imidazol-4-yl)-1-phenyl-1H-pyrazol-5-amine hydrochloride (2 g, 6.90 mmol) was dissolved in 100 mL of CHCl_3 and pyridine (6.386 mL, 78.96 mmol) was added followed by phenylchloroformate (2.972 mL, 23.69 mmol). The reaction was stirred at ambient for 2 hours and quenched with 1N NaOH (100 mL). The layers were separated and the aqueous layer was washed with DCM. The combined organic extracts were dried (MgSO_4) and concentrated. The crude material was purified by silica gel column chromatography, eluting with 25-100% acetone/hexanes, to afford the title compound (2.35 g, 4.752 mmol, 68.8 % yield). MS (apci) $m/z = 494.1$ (M+H). This intermediate needs to be reacted with two equivalents of an amine to afford the desired urea products.

Intermediate 10



5-amino-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide

[00602] Step A: Preparation of ethyl 3-cyano-2-oxobutanoate: To a solution of lithium bis(trimethylsilyl)amide (1M in THF, 46.4 mL, 46.39 mmol) in THF (100 mL) under N_2 at -78 °C was added propiononitrile (3.08 mL, 53.01 mmol) dropwise over 2 min. The mixture was stirred at -78 °C for 1 hour, then diethyl oxalate (6.0 mL, 44.18 mmol) was added dropwise over 5 minutes. The reaction mixture was stirred at -78 °C for 45 minutes, then at 0 °C for 4 hours, then was diluted with H_2O (100 mL) and extracted with Et_2O (100 mL). The aqueous phase was neutralized with 6M HCl (7 mL), then extracted with Et_2O (3 x 100 mL), and the combined

organic extracts were washed with brine (100 mL), dried (MgSO₄), filtered, and concentrated to afford the product as a yellow syrup (6.6 g, 96% yield). ¹H NMR (CDCl₃) δ 4.46 (q, 2H), 4.38 (dq, 1H), 1.44 (t, 3H), 1.38 (dt, 3H) ppm.

[00603] Step B: Preparation of ethyl 5-amino-4-methyl-1-phenyl-1H-pyrazole-3-carboxylate:

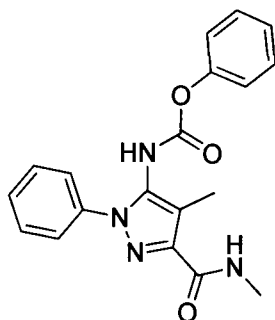
To a suspension of phenylhydrazine hydrochloride (6.15 g, 42.54 mmol) in EtOH (150 mL) was added ethyl 3-cyano-2-oxobutanoate (6.6 g, 42.54 mmol). The reaction mixture was heated to reflux for 16 hours, then cooled to ambient temperature. The reaction mixture was diluted with saturated aqueous NaHCO₃ (50 mL), extracted with DCM (3 x 100 mL), and the combined organic phases were dried (MgSO₄), filtered and concentrated under vacuum. The crude product was purified by silica column chromatography, eluting with 0-60% acetone in hexanes to afford the product as a yellow solid (7.1 g, 68 % yield). MS (apci) m/z = 246.1 (M+H).

[00604] Step C: Preparation of 5-amino-4-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid:

To a solution of ethyl 5-amino-4-methyl-1-phenyl-1H-pyrazole-3-carboxylate (1.52 mg, 6.21 mmol) in THF (12 mL) and MeOH (6 mL) was added LiOH (2M aq, 9.31 mL, 18.6 mmol). The reaction mixture was stirred at ambient temperature for 19 hours, then partially concentrated under reduced pressure, then neutralized with 6M HCl (3.2 mL), extracted with 10:90 MeOH/DCM (3 x 25 mL), and the combined organic extracts were washed with brine (50 mL), dried (MgSO₄), filtered and concentrated to give the title compound as a yellow solid (1.3 g, 96% yield). MS (apci) m/z = 218.1 (M+H).

[00605] Step D: Preparation of 5-amino-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide: To a solution of 5-amino-4-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid (223 mg, 1.02 mmol) in acetonitrile (10 mL) were added DIEA (0.71 mL, 4.10 mmol), methanamine hydrochloride (138 mg, 2.05 mmol), DMF (2 mL), followed by addition of HATU (428 mg, 1.13 mmol). The reaction mixture was stirred at ambient temperature for 19 hours and then partially concentrated under reduced pressure. The mixture was purified by reverse-phase column chromatography, eluting with 5-60% acetonitrile/water to afford the title compound as a pale yellow solid (182 mg, 77% yield). MS (apci) m/z = 231.1 (M+H).

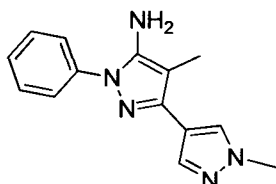
Intermediate 11



Phenyl 4-methyl-3-(methylcarbamoyl)-1-phenyl-1H-pyrazol-5-ylcarbamate

[00606] Prepared by the method as described for Intermediate 1 using 5-amino-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide instead of 3-methyl-1-phenyl-1H-pyrazol-5-amine. The crude material (75.6 mg, 0.2158 mmol, 99.4% yield) was used without purification. MS (apci) $m/z = 351.1$ (M+H).

Intermediate 12



1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-amine

[00607] Step A: ethyl 1-methyl-1H-pyrazole-4-carboxylate: To a 3000-mL three-necked flask was added ethyl 2-formyl-3-oxopropanoate (100 g, 694 mmol), followed by anhydrous 200-proof EtOH (694 mL) to obtain a clear yellowish solution. The reaction was cooled in an ice bath to 5 °C, and then methylhydrazine (35.8 mL, 680 mmol) was added dropwise. A vigorous exotherm was observed during hydrazine addition and the temperature was kept below 12 °C by controlling the addition rate. After the hydrazine addition was complete, the ice bath was removed, and the reaction was allowed to stir at ambient temperature overnight. The reaction was concentrated on a rotary evaporator to a crude orange oil. The crude was taken up in DCM and re-concentrated, then on high vacuum for 2 days to yield the title compound as a tan orange oil (106 g, 99.1% yield).

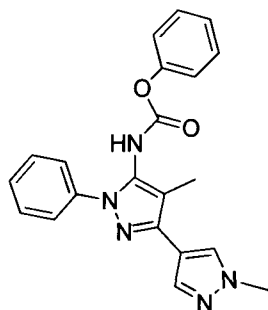
[00608] Step B: 2-methyl-3-(1-methyl-1H-pyrazol-4-yl)-3-oxopropanenitrile: To a four-necked 5-liter round bottomed flask fitted with an overhead stirrer and addition funnel was charged LHMDs (1444 mL, 1444 mmol) (1.0M in THF). The solution was cooled in an acetone/dry ice bath (internal temperature of -79 °C) under nitrogen, followed by slow addition of propiononitrile (103 mL, 1444 mmol) via dropping funnel. The mixture was stirred at -80 °C for 90 minutes. A solution of ethyl 1-methyl-1H-pyrazole-4-carboxylate (106 g, 688 mmol) in anhydrous THF (500 mL) was then introduced dropwise via an addition funnel (addition time: about 45 minutes; internal temperature during addition remained below -76 °C). After the addition was complete, the reaction was allowed to slowly warm to ambient temperature and stirred overnight. An orange glass deposited on the bottom of the flask. The organics were decanted and the orange glass was dissolved in warm water. The aqueous mixture was washed with ether (3 x 1000 mL). The aqueous phase was then pH-adjusted to 5 (pH paper) using concentrated HCl and saturated bicarbonate solution. The aqueous layer was extracted with DCM (3 x 1000 mL). The combined organic extracts were dried over MgSO₄, filtered and

concentrated to yield 2-methyl-3-(1-methyl-1H-pyrazol-4-yl)-3-oxopropanenitrile as an amber oil (92 g, 82 % yield). MS (apci) m/z = 162.1 (M-H).

[00609] Step C: 1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-amine: A 3L, 3 necked round bottomed flask was charged with 2-methyl-3-(1-methyl-1H-pyrazol-4-yl)-3-oxopropanenitrile (60 g, 368 mmol) absolute anhydrous ethanol (1000 mL) and phenylhydrazine hydrochloride (58 g, 404 mmol) at ambient temperature to form a yellowish suspension. The reaction vessel was equipped with a water condenser and refluxed (using a heating mantle) overnight. The reaction was concentrated and 1M NaOH (1L) was added and the solid was broken up and collected. The solid was washed with water and hexanes. A second crop crashed out in the filtrate and was collected. The combined solids were crushed and triturated with ether (500 mL). The solid was collected filtration, washed with hexanes and air dried under vacuum to provide 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-amine (93 g, 100 % yield).

[00610] Step D: phenyl 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-ylcarbamate: In a 3 L, round bottomed flask was charged with 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-amine (50 g, 197.4 mmol) and EtOAc (1000 mL) to obtain a clear brownish solution. To this was added NaOH (2M aq) (500 mL) in one portion to obtain a turbid mixture (both the aqueous and organic layers were clear but a precipitate was observed in between the two layers). After 3 minutes, phenyl carbonochloridate (74.29 mL, 592.2 mmol) was added slowly at ambient temperature exotherm to 33 °C. The reaction stirred at ambient temperature for 2 hours. Additional phenyl carbonochloridate (10 mL) was added. After 30 minutes the organics were separated, washed with brine and concentrated under vacuum. The product was purified by silica gel chromatography (eluting with 75% ethyl acetate in hexanes) to provide phenyl 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-ylcarbamate (60 g, 81.4% yield).

Intermediate 13

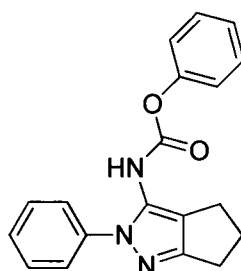


phenyl (1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)carbamate

[00611] A 3 L, round bottomed flask was charged with 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-amine (50 g, 197.4 mmol) and EtOAc (1000 mL) to obtain a clear brownish solution. To this was added aqueous NaOH (2M; 500 mL) in one portion to obtain a turbid

mixture (the aqueous and organic layers were clear, but a precipitate was observed in between the two layers). After 3 minutes, phenyl carbonochloridate (74.29 mL, 592.2 mmol) was added slowly at ambient temperature (the temperature of the reaction mixture increased to 33 °C during the addition). The reaction stirred at ambient temperature for 2 hours. Additional phenyl carbonochloridate (10 mL) was added. After 30 minutes the organics layers were separated, washed with brine and concentrated under vacuum. The residue was purified by silica gel chromatography (eluting with 75% ethyl acetate in hexanes) to provide phenyl 1',4'-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-ylcarbamate (60 g, 81.4% yield).

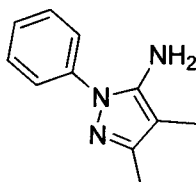
Intermediate 14



phenyl (2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)carbamate

[00612] A suspension of 2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-amine (6.0 g, 30.11 mmol) in EtOAc (250 mL) was first cooled in ice bath, followed by addition of NaOH (2N aq, 30.11 mL, 60.23 mmol) in one portion and then PhOCOCl (6.800 mL, 54.20 mmol) drop-wise. The reaction was warmed up to ambient temperature and stirred for 18 hours. The reaction mixture was diluted with EtOAc (100 mL) and phase-separated. The organic layer was washed with water (2 × 150 mL) and brine (150 mL), dried (MgSO₄), filtered and concentrated. The crude was taken up in DCM and concentrated to dryness. The crude solid was triturated with ether/hexanes (2:1, 2 × 100 mL), filtered and dried, to provide the product as an off-white solid (7.4 g, 77 % yield). MS (apci) m/z = 320.1 (M+H).

Intermediate 15

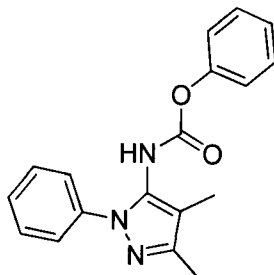


3,4-dimethyl-1-phenyl-1H-pyrazol-5-amine

[00613] To a solution of 2-methyl-3-oxobutanenitrile (295 mg, 3.038 mmol) in EtOH (40 mL) were added HCl (5-6M in iPrOH, 0.6 mL) and phenylhydrazine (0.299 mL, 3.038 mmol). The reaction mixture was heated at reflux for 17 hours, then cooled to ambient temperature. The reaction mixture was diluted with saturated aqueous NaHCO₃ (20 mL), extracted with DCM (2 x

25 mL), and the combined organic phases were dried (MgSO₄), filtered and concentrated. The crude product was purified by silica column chromatography, eluting with 0-3% MeOH/DCM to yield the product as a tan solid (555 mg, 97% yield). MS (apci) m/z = 188.2 (M+H).

Intermediate 16



phenyl 3,4-dimethyl-1-phenyl-1H-pyrazol-5-ylcarbamate

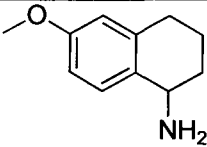
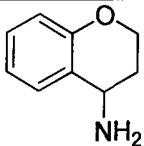
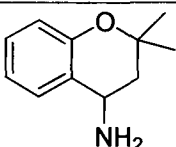
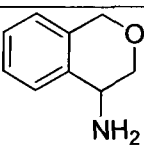
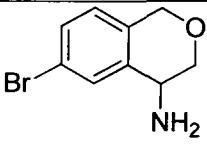
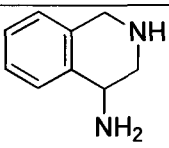
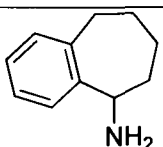
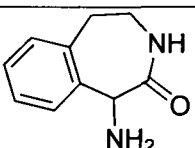
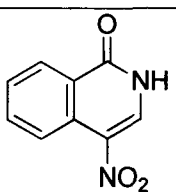
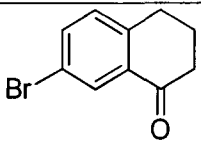
[00614] Prepared by the method as described for Intermediate 1, using 3,4-dimethyl-1-phenyl-1H-pyrazol-5-amine instead of 3-methyl-1-phenyl-1H-pyrazol-5-amine. The crude product (0.933 g, 3.036 mmol, quantitative yield) was used without purification. MS (apci) m/z = 308.1 (M+H).

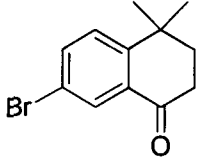
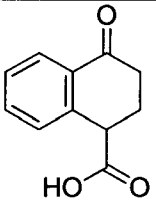
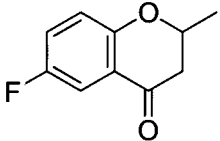
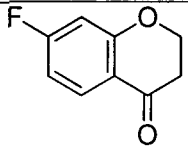
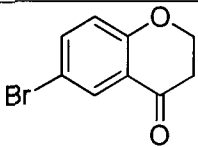
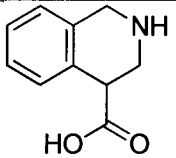
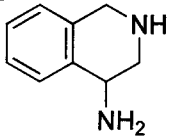
Synthetic Examples

[00615] Table 1 provides a list of commercially available compounds that were used in the synthesis of intermediates and examples.

Table 1

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	Ryan Scientific, Inc., EN300-14400	89399-92-8
	Combi-Blocks, Inc., HI-1327	5346-56-5
	Aldrich/24,782-0	2217-40-5
	Lancaster Synthesis Inc./ 17022	23357-52-0
	Aldrich/668,818	21966-60-9

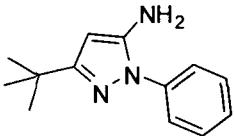
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	J & W PharmLab, LLC/20-1070	53981-38-7
	Matrix Scientific/021506	N/A
	Activate Scientific/D4046	147663-00-1
	Activate Scientific /AS2094G1	N/A
	AstaTech, Inc./52240	486453-50-3
	Ryan Scientific, Inc./EN400-13090	N/A
	APAC Pharmaceutical/552625	253185-43-2
	Ubichem plc/cat# UB-10298	N/A
	Maybridge/MO 01275	32281-97-3

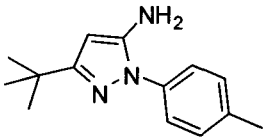
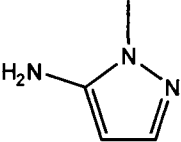
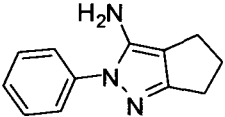
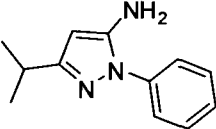
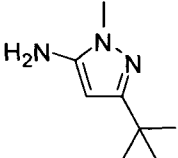
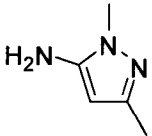
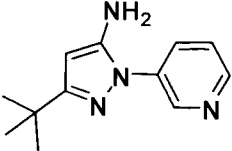
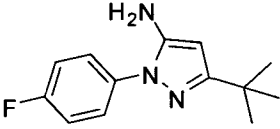
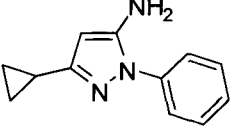
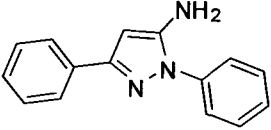
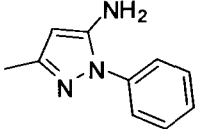
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	Chemgenx, LLC/CX-01571	113209-68-0
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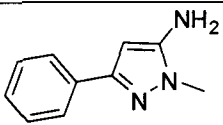
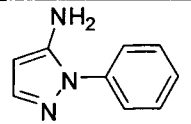
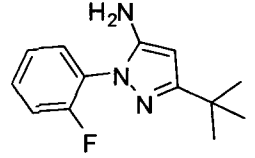
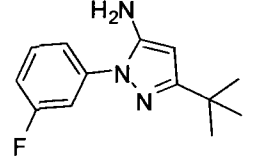
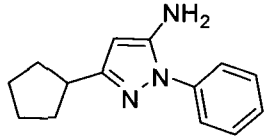
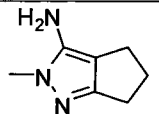
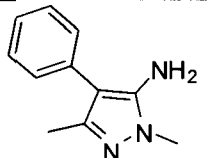
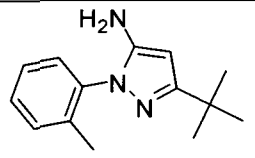
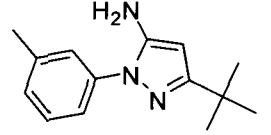
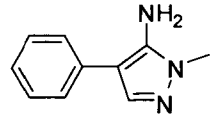
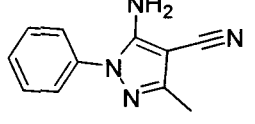
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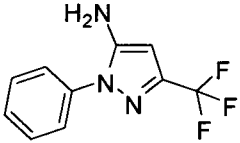
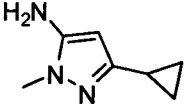
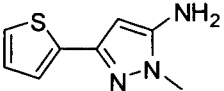
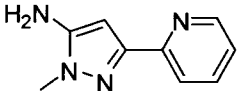
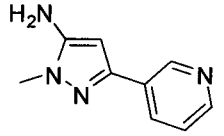
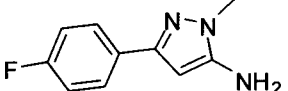
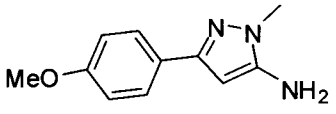
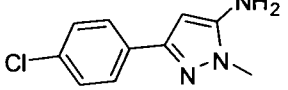
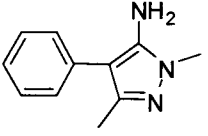
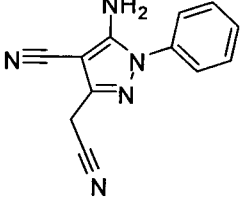
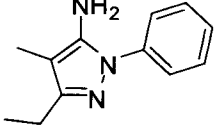
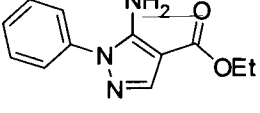
[00616] Table 1 provides a list of commercially available pyrazole intermediates can be used in the synthesis of compounds described in the Examples.

Table 1

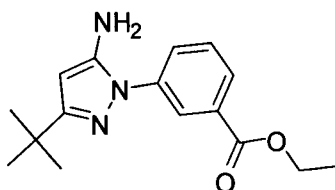
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	Oakwood, 021512	126208-61-5

Pyrazole	Vendor/Catalog#	CAS#
	Array BioPharma, A1075-0	N/A
	Maybridge, GK03066	1192-21-8
	Ryan Scientific, EN300-14400	89399-92-8
	Oakwood, 021516	N/A
	Alfa Aesar, AAB20095-06	118430-73-2
	Aldrich, 532223	3524-32-1
	Accela ChemBio Chem Co, SY003755	876299-97-7
	ChemImpex, 18122	778611-16-8
	Oakwood, 017105	175137-45-8
	Alfa Aesar, AAB20464-06	5356-71-8
	Aldrich, 541001	1131-18-6

Pyrazole	Vendor/Catalog#	CAS#
	Alfa Aesar, AAA15754-06	10199-50-5
	TCI America, A0174	826-85-7
	Oakwood, 023890	N/A
	J&W Pharmalab, 68-0035S	1187931-80-1
	VWR, EN300-09508	N/A
	ChemBridge, 4019184	885529-68-0
	ChemBridge, 4001950	N/A
	ChemImpex, 19156	337533-96-7
	ChemImpex, 19155	898537-77-4
	ChemBridge, 4006072	N/A
	Oakwood, 005982	5346-56-5

Pyrazole	Vendor/Catalog#	CAS#
	ChemImpex, 18771	182923-55-3
	Maybridge, KM00278	118430-74-3
	Maybridge, KM00835	118430-78-7
	ChemBridge, 4015288	N/A
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	Matrix, 020274	N/A
	Matrix, 019183	N/A
	Maybridge, KM 04038	126417-82-1
	ChemBridge, 4001950	N/A
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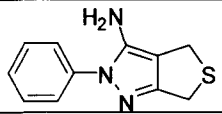
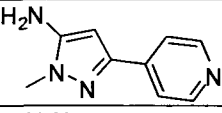
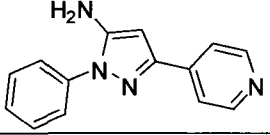
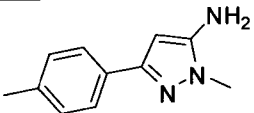
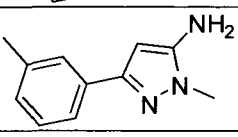
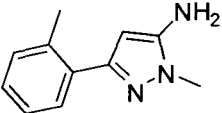
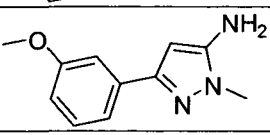
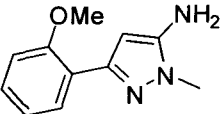
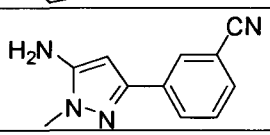
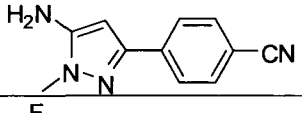
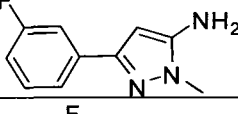
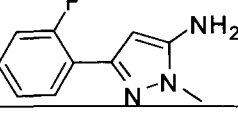
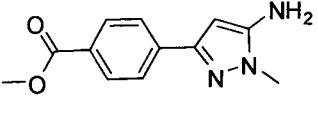
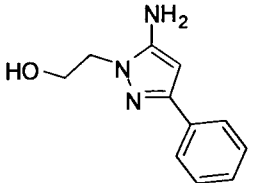
Intermediate P1**Ethyl 3-(5-amino-3-tert-butyl-1H-pyrazol-1-yl)benzoate**

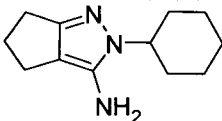
[00617] To a suspension of ethyl 3-hydrazinylbenzoate hydrochloride (500 mg, 2.31 mmol) in EtOH (20 mL) was added 4,4-dimethyl-3-oxopentanenitrile (318 mg, 2.54 mmol). The reaction mixture was heated to reflux for 18 hours, then cooled to ambient temperature and concentrated *in vacuo*. The crude product was purified by silica column chromatography, eluting with 0-5% MeOH/DCM to yield the product as a yellow oil (154 mg, 23% yield). MS (apci) m/z = 288.2 (M+H).

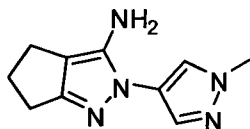
[00618] The compounds in Table 2 were prepared by the method as described for Intermediate P1, substituting 4,4-dimethyl-3-oxopentanenitrile with the appropriate cyanoketone and ethyl 3-hydrazinylbenzoate hydrochloride with the appropriate hydrazine.

Table 2

Intermediate #	Structure	Data
P2		MS (apci) m/z = 188.2 (M+H)
P3		MS (apci) m/z = 218.1 (M+H)
P4		MS (apci) m/z = 218.2 (M+H)
P5		MS (apci) m/z = 188.2 (M+H)
P6		MS (apci) m/z = 214.2 (M+H)
P7		MS (apci) m/z = 188.2 (M+H)
P8		MS (apci) m/z = 301.0 (M+H)

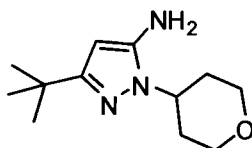
Intermediate #	Structure	Data
P9		MS (apci) m/z = 218.1 (M+H)
P10		MS (apci) m/z = 175.2 (M+H)
P11		MS (apci) m/z = 237.3 (M+H)
P12		MS (apci) m/z = 188.2 (M+H)
P13		MS (apci) m/z = 188.2 (M+H)
P14		MS (apci) m/z = 188.2 (M+H)
P15		MS (apci) m/z = 204.2 (M+H)
P16		MS (apci) m/z = 204.2 (M+H)
P17		MS (apci) m/z = 199.0 (M+H)
P18		MS (apci) m/z = 199.1 (M+H)
P19		MS (apci) m/z = 192.2 (M+H)
P20		MS (apci) m/z = 192.2 (M+H)
P21		MS (apci) m/z = 232.2 (M+H)
P22		MS (apci) m/z = 204.2 (M+H)

Intermediate #	Structure	Data
P23		MS (apci) m/z = 206.1 (M+H)

Intermediate P1012-(1-methyl-1H-pyrazol-4-yl)-2,4,5,6-tetrahydrocyclopenta-[c]pyrazol-3-amine

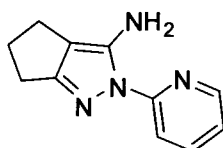
[00619] Step A: Preparation of di-tert-butyl 1-(1-methyl-1H-pyrazol-4-yl)hydrazine-1,2-dicarboxylate: To a solution of 4-bromo-1-methyl-1H-pyrazole (1.93 mL, 18.6 mmol) in ether (37.3 mL) cooled to -78 °C was added nBuLi (23.3 mL, 37.3 mmol). After stirring at -78 °C for 30 minutes, a solution of di-t-butyl azodicarboxylate (4.29 g, 18.6 mmol) in Et₂O (37.3 mL, 18.6 mmol) was added dropwise. After 1 hour, the reaction mixture was warmed up to -20 °C and quenched with ice. After warming to ambient temperature, the mixture was filtered and rinsed with Et₂O. The resulting solid was taken up in a mixture of DCM and water, and the mixture was phase separated. The organic layer was dried with MgSO₄, filtered and concentrated *in vacuo* to afford the first batch of product as a white solid (1.64 g, 28% yield). A second batch of product was recovered from the filtrate by silica column chromatography, eluting with 40-60% hexanes/EtOAc (0.51 g, 8.8% yield). MS (apci) m/z = 313.0 (M+H).

[00620] Step B: Preparation of 2-(1-methyl-1H-pyrazol-4-yl)-2,4,5,6-tetrahydrocyclopenta-[c]pyrazol-3-amine: To a solution of di-tert-butyl 1-(1-methyl-1H-pyrazol-4-yl)hydrazine-1,2-dicarboxylate (103 mg, 0.330 mmol) in EtOH (1.65 mL, 0.330 mmol) was added concentrated HCl (137 µL, 1.65 mmol). The mixture was stirred at ambient temperature for 5 minutes, then cooled in an ice bath followed by addition of 2-oxocyclopentanecarbonitrile (36.0 mg, 0.330 mmol). After stirring for 5 minutes, the reaction mixture was warmed to ambient temperature overnight. The reaction mixture was concentrated and partitioned in water and DCM. After phase-separation, the aqueous layer was basified (pH 10) and then extracted with DCM (3 × 10 mL). The combined organic extracts were dried with MgSO₄, filtered and concentrated *in vacuo*. The crude material was purified by reverse-phase column chromatography, eluting with 0-100% acetonitrile/water to afford the product as a yellow solid (4.5 mg, 6.7% yield). MS (apci) m/z = 204.1 (M+H).

Intermediate P1023-tert-butyl-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-5-amine

[00621] Step A: Preparation of (tetrahydro-2H-pyran-4-yl)hydrazine hydrochloride: A suspension of dihydro-2H-pyran-4(3H)-one (2.00 g, 20.0 mmol) and *tert*-butyl hydrazinecarboxylate (2.64 g, 20.0 mmol) in hexanes (20.0 mL) was refluxed for 2 hours. After cooling, BH₃-THF complex (20.0 mL, 20.0 mmol) was added and the reaction mixture was stirred for 1 hour. The mixture was then treated with 4 N HCl in dioxane (20.0 mL, 79.9 mmol), followed by 3 drops of water. After stirring at ambient temperature for 1 hour, the reaction mixture was filtered and rinsed with EtOAc to afford the product as a solid (2.39 g, 78.4% yield). MS (apci) *m/z* = 117.0 (M+H).

[00622] Step B: Preparation of 3-tert-butyl-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-5-amine: Prepared by the method as described in for the preparation of Intermediate P1, substituting (tetrahydro-2H-pyran-4-yl)hydrazine dihydrochloride for ethyl 3-hydrazinylbenzoate hydrochloride to yield the product as a yellow oil (0.472 g, 99.9% yield). MS (apci) *m/z* = 224.1 (M+H).

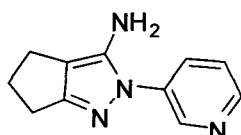
Intermediate P1032-(pyridin-2-yl)-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-amine

[00623] Step A: Preparation of 2-(2-(pyridin-2-yl)hydrazono)cyclopentane-carbonitrile: A solution of 2-hydrazinylpyridine (0.200 g, 1.83 mmol) and 2-oxocyclopentanecarbonitrile (0.200 g, 1.83 mmol) in MeOH (9.16 mL) was treated with concentrated HCl (0.764 mL, 9.16 mmol) and refluxed for 16 hours. The reaction mixture was concentrated *in vacuo*, and then partitioned in water and DCM. After phase-separation, the aqueous layer was washed with DCM, basified (saturated NaHCO₃, pH 10), and extracted with DCM. The combined organic layers were dried with MgSO₄, filtered and concentrated. The crude material was purified by silica column chromatography, eluting with 100% EtOAc to afford the product (0.289 g, 78.6% yield). MS (apci) *m/z* = 201.2 (M+H).

[00624] Step B: Preparation of 2-(pyridin-2-yl)-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-amine: A solution of 2-(2-(pyridin-2-yl)hydrazono)cyclopentanecarbonitrile (0.243 g, 1.21

mmol) in EtOH (6.06 mL, 1.21 mmol) was treated with 6 M HCl (0.202 mL, 1.21 mmol) and refluxed for 3 days. After removal of the solvent, the crude residue was diluted in water, basified (saturated NaHCO₃, pH 10) and extracted with DCM. The combined organic layers were dried with MgSO₄, filtered and concentrated. The crude material was purified by silica column chromatography, eluting with 50% EtOAc/hexanes to afford the product (0.198 g, 81.6% yield). MS (apci) m/z = 201.2 (M+H).

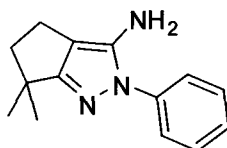
Intermediate P104



2-(pyridin-3-yl)-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-amine

[00625] Prepared by the method described above for Intermediate P103, substituting 3-hydrazinylpyridine for 2-hydrazinyl pyridine to afford the title product. MS (apci) m/z = 201.1 (M+H).

Intermediate P105



6,6-dimethyl-2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-amine

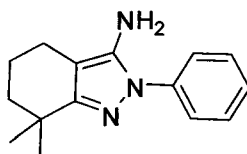
[00626] Step A: Preparation of 5-chloro-2,2-dimethylpentanenitrile: Isobutyronitrile (1.38 g, 20.0 mmol) and 1-bromo-3-chloropropane (3.46 g, 22.0 mmol) were sequentially added to a 1 M solution of lithium bis(trimethylsilyl)amide (20.0 mL, 20.0 mmol) while stirring. After stirring at 70 °C for 16 hours, the reaction mixture was quenched with water then extracted with DCM. The combined organic layers were dried with MgSO₄, filtered and concentrated *in vacuo* to afford 5-chloro-2,2-dimethylpentanenitrile (2.91 g, 100% yield). ¹H NMR (CDCl₃) δ 3.57-3.61 (m, 2H), 1.94-2.02 (m, 2H), 1.67-1.72 (m, 2H), 1.37 (s, 6H).

[00627] Step B: Preparation of 2,2-dimethylhexanedinitrile: A suspension of 5-chloro-2,2-dimethylpentanenitrile (2.91 g, 20.0 mmol) and NaCN (1.57 g, 32.0 mmol) in DMF (20.0 mL) and water (1 mL) was heated at 100 °C for 16 hours. After cooling, the reaction mixture was diluted with water and refluxed for 30 minutes, then cooled, poured into water and stirred for 3 hours. The solution was then extracted with Et₂O. The combined Et₂O extracts were washed with H₂O, dried with MgSO₄, filtered and concentrated *in vacuo* to afford the product (2.20 g, 80.7% yield). ¹H NMR (CDCl₃) δ 2.42-2.47 (m, 2H), 1.83-1.92 (m, 2H), 1.67-1.72 (m, 2H), 1.39 (s, 6H).

[00628] Step C: Preparation of 3,3-dimethyl-2-oxocyclopentanecarbonitrile: A suspension of KOtBu (0.511 g, 4.55 mmol) in toluene (18.4 mL) was treated a toluene (2.0 mL) solution of 2,2-dimethylhexanedinitrile (1.00 g, 7.34 mmol) and heated at 80 °C for 2 hours. The reaction mixture was then cooled to ambient temperature and quenched with water. The mixture was separated and the organic layer was stirred in 2 N HCl (20 mL) for 16 hours. The mixture was separated and the organic layer dried with MgSO₄, filtered and concentrated *in vacuo* to a yellow-white solid. The crude solid was purified by silica column chromatography, eluting with 10-40% EtOAc/hexanes, to afford the product (0.250 g, 24.8% yield). ¹H NMR (CDCl₃) δ 3.20-3.26 (m, 1H), 2.38-2.47 (m, 1H), 2.14-2.25 (m, 1H), 1.97-2.05 (m, 1H), 1.74-1.83 (m, 1H), 1.14 (s, 6H).

[00629] Step D: Preparation of 6,6-dimethyl-2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-amine: Prepared by the method as described for Intermediate P1, substituting phenylhydrazine for ethyl 3-hydrazinylbenzoate hydrochloride and 3,3-dimethyl-2-oxocyclopentanecarbonitrile for 4,4-dimethyl-3-oxopentanenitrile to afford the product (0.192 g, 46.2% yield) as a yellow solid. MS (apci) m/z = 228.2 (M+H).

Intermediate P106



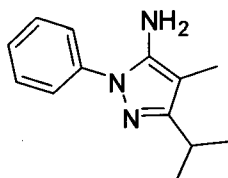
7,7-dimethyl-2-phenyl-4,5,6,7-tetrahydro-2H-indazol-3-amine

[00630] Step A: Preparation of 2,2-dimethylheptanedinitrile: Prepared by the method as described for Intermediate P105, Steps A and B, substituting 1-bromo-4-chlorobutane for 1-bromo-3-chloropropane to yield the product (2.21 g, 73.7% yield). ¹H NMR (CDCl₃) δ 2.37-2.42 (m, 2H), 1.53-1.77 (m, 6H), 1.36 (s, 6H).

[00631] Step B: Preparation of 3,3-dimethyl-2-oxocyclohexanecarbonitrile: A suspension of KOtBu (0.463 g, 4.13 mmol) in toluene (16.6 mL) was treated with a solution of 2,2-dimethylheptanedinitrile (1.00 g, 6.66 mmol) in toluene (2.0 mL) and heated at 80 °C for 48 hours. After cooling to ambient temperature, the reaction mixture was quenched with water and phase-separated, and the organic layer was stirred with 2 N HCl (20 mL) for 16 hours. After phase-separation, the organic layer was dried with MgSO₄, filtered and concentrated *in vacuo*. The crude material was purified by silica column chromatography, eluting with 10-20% EtOAc/hexanes to afford the product (0.374 g, 37.2% yield). ¹H NMR (CDCl₃) δ 3.72-3.78 (m, 1H), 2.42-2.50 (m, 1H), 1.78-2.04 (m, 4H), 1.60-1.70 (m, 1H), 1.21 (s, 3H), 1.16 (s, 3H).

[00632] Step C: Preparation of 7,7-dimethyl-2-phenyl-4,5,6,7-tetrahydro-2H-indazol-3-amine: Prepared by the method as described for Intermediate P1, substituting phenylhydrazine for ethyl 3-hydrazinylbenzoate hydrochloride and 3,3-dimethyl-2-oxocyclohexanecarbonitrile for 4,4-dimethyl-3-oxopentanenitrile to yield the product as an off-white solid (0.490 g, 54.2% yield, 66% purity). MS (apci) m/z = 242.2 (M+H).

Intermediate P107

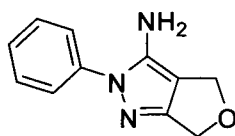


3-isopropyl-4-methyl-1-phenyl-1H-pyrazol-5-amine

[00633] Step A: Preparation of 2,4-dimethyl-3-oxopentanenitrile: To a solution of propiononitrile (518 mg, 9.40 mmol) in THF (50 mL, 7.83 mmol) at -78 °C under N₂ was slowly added lithium bis(trimethylsilyl)amide (1M in THF) (7.83 mL, 7.83 mmol). After 30 minutes, methyl isobutyrate (0.898 mL, 7.83 mmol) was added dropwise, and the reaction mixture was warmed to 0 °C. A yellow precipitate formed, the reaction mixture was stirred for 1 hour, then diluted with H₂O (50 mL) to dissolve the solids. The mixture was extracted with Et₂O (25 mL), and the basic aqueous phase was acidified with 2M HCl (5 mL) and extracted with Et₂O (2 x 50 mL). The combined organic phases were washed with brine (50 mL), dried with MgSO₄, filtered, and concentrated to afford the product (421 mg, 42.9% yield)

[00634] Step B: Preparation of 3-isopropyl-4-methyl-1-phenyl-1H-pyrazol-5-amine: Prepared by the method as described for Intermediate P1, substituting phenyl hydrazine for ethyl 3-hydrazinylbenzoate hydrochloride and 4,4-dimethyl-3-oxopentanenitrile with 2,4-dimethyl-3-oxopentanenitrile to yield the product as a yellow syrup (0.587 g, 81.1% yield). MS (apci) m/z = 216.2 (M+H).

Intermediate P108



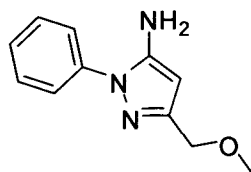
2-phenyl-4,6-dihydro-2H-furo[3,4-c]pyrazol-3-amine

[00635] Step A: Preparation of 4-oxotetrahydrofuran-3-carbonitrile: To a suspension of KOtBu (996.6 mg, 8.881 mmol) in THF (640.4 mg, 8.881 mmol) cooled to 0 °C was added dropwise methyl 2-hydroxyacetate (675.7 μ L, 8.881 mmol) and stirred for 10 minutes. The acrylonitrile (589.1 μ L, 8.881 mmol) was then added and the reaction stirred at ambient temperature. After 3 hours, the reaction was diluted with H₂O (50 mL), then extracted with

Et₂O (25 mL) to remove any starting ester. The basic aqueous phase was acidified with 2M HCl (5 mL), then extracted with Et₂O (2 x 50 mL). The combined organic phases were dried with MgSO₄, filtered, and concentrated to afford a light brown oil (446 mg, 45.2% yield). ¹H NMR (CDCl₃) δ 4.63 (t, 1H), 4.24 (t, 1H), 4.14 (d, 1H), 4.02 (d, 1H), 3.57 (t, 1H).

[00636] Step B: Preparation of 2-phenyl-4,6-dihydro-2H-furo[3,4-c]pyrazol-3-amine: Prepared by the method as described for Intermediate P1, substituting phenyl hydrazine for ethyl 3-hydrazinylbenzoate hydrochloride and 4,4-dimethyl-3-oxopentanenitrile with 4-oxotetrahydrofuran-3-carbonitrile to yield the product as a reddish-brown syrup (182 mg, 22.5% yield). MS (apci) m/z = 202.1 (M+H).

Intermediate P109

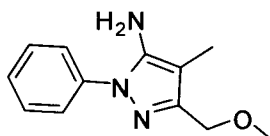


3-(methoxymethyl)-1-phenyl-1H-pyrazol-5-amine

[00637] Step A: Preparation of 4-methoxy-3-oxobutanenitrile: To a solution of methyl 2-methoxyacetate (0.4753 mL, 4.803 mmol) in THF (20 mL, 4.803 mmol) at -78 °C under N₂ was added acetonitrile (0.3033 mL, 5.763 mmol), followed by lithium bis(trimethylsilyl)amide (1M in THF) (4.803 mL, 4.803 mmol). After stirring 1 hour, the reaction mixture was warmed to 0 °C and stirred for 1 hour. The reaction mixture was then diluted with H₂O (25 mL), washed with Et₂O (25mL), then neutralized with 2 M HCl (1.5 mL). This was extracted with Et₂O (2 x 25 mL) and the combined organic phases were washed with brine (25 mL), dried with MgSO₄, filtered, and concentrated to afford the product (169 mg, 31.1% yield). ¹H NMR (CDCl₃) δ 4.09 (s, 2H), 3.66 (s, 2H), 3.46 (s, 3H)

[00638] Step B: Preparation of 3-(methoxymethyl)-1-phenyl-1H-pyrazol-5-amine: Prepared by the method as described for Intermediate P1, substituting phenyl hydrazine for ethyl 3-hydrazinylbenzoate hydrochloride and 4,4-dimethyl-3-oxopentanenitrile with 4-methoxy-3-oxobutanenitrile to yield the product as a pale yellow residue (6.0 mg, 2.0% yield). MS (apci) m/z = 204.0 (M+H).

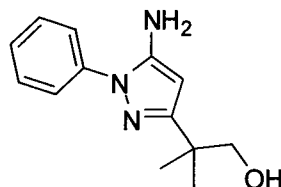
Intermediate P110



3-(methoxymethyl)-4-methyl-1-phenyl-1H-pyrazol-5-amine

[00639] Prepared according to the method as described for Intermediate P109, replacing acetonitrile with propionitrile to afford the product as an orange residue. MS (apci) m/z = 218.0 (M+H).

Intermediate P111



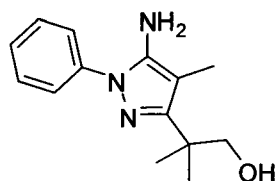
2-(5-amino-1-phenyl-1H-pyrazol-3-yl)-2-methylpropan-1-ol

[00640] Step A: Preparation of methyl 3-(tert-butyldimethylsilyloxy)-2,2-dimethylpropanoate: Methyl 3-hydroxy-2,2-dimethylpropanoate (1.000 g, 7.567 mmol), TBDMS-Cl (1.140 g, 7.567 mmol) and imidazole (0.5666 g, 8.323 mmol) were dissolved in DMF (5 mL, 7.567 mmol) and stirred at ambient temperature overnight. The reaction mixture was diluted with H₂O (25 mL) and extracted with EtOAc (2 x 25mL). The combined organic phases were washed with brine (25 mL), dried with MgSO₄, filtered and concentrated to afford the product (1.92 g, 103% yield). ¹H NMR (CDCl₃) δ 3.66 (s, 3H), 3.57 (s, 2H), 1.15 (s, 6H), 0.87 (s, 9H), 0.02 (s, 6H).

[00641] Step B: Preparation of 5-(tert-butyldimethylsilyloxy)-4,4-dimethyl-3-oxopentanenitrile: Prepared according to the method described for Intermediate P109, replacing methyl 2-methoxyacetate with methyl 3-(tert-butyldimethylsilyloxy)-2,2-dimethylpropanoate to afford the product as a pale yellow residue. ¹H NMR (CDCl₃) δ 3.70 (s, 2H), 3.55 (s, 2H), 1.15 (s, 6H), 0.89 (s, 9H), 0.06 (s, 6H).

[00642] Step C: Preparation of 2-(5-amino-1-phenyl-1H-pyrazol-3-yl)-2-methylpropan-1-ol: Prepared by the method as described for Intermediate P1, substituting phenyl hydrazine for ethyl 3-hydrazinylbenzoate hydrochloride and 4,4-dimethyl-3-oxopentanenitrile with methyl 3-(tert-butyldimethylsilyloxy)-2,2-dimethylpropanoate to yield the product as yellow syrup (74 mg, 66% yield). MS (apci) m/z = 232.2 (M+H).

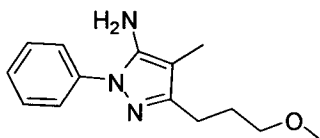
Intermediate P112



2-(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)-2-methylpropan-1-ol

[00643] Prepared according to the method described for Intermediate P111, replacing acetonitrile with propionitrile to afford the product as a yellow residue. MS (apci) $m/z = 246.2$ (M+H).

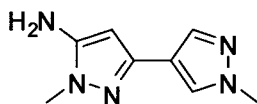
Intermediate P113



3-(3-methoxypropyl)-4-methyl-1-phenyl-1H-pyrazol-5-amine

[00644] Prepared according to the method described for Intermediate P109, replacing methyl 2-methoxyacetate with methyl 4-methoxybutanoate and replacing acetonitrile with propionitrile in Step A to afford the product as an orange-brown syrup. MS (apci) $m/z = 246.1$ (M+H).

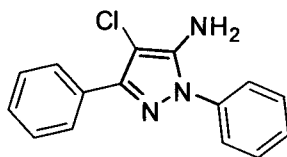
Intermediate P114



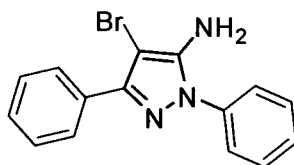
1,1'-dimethyl-1H,1'H-3,4'-bipyrazol-5-amine

[00645] Step A: Preparation of 3-(1-methyl-1H-pyrazol-4-yl)-3-oxopropanenitrile: A solution of ethyl 1-methyl-1H-pyrazole-4-carboxylate (500 mg, 3.24 mmol), toluene (7.50 mL, 70.4 mmol), and acetonitrile (346 μ L, 6.49 mmol) was treated in one portion with KOtBu (1092 mg, 9.73 mmol) to give a hazy solution. The reaction was allowed to stir at ambient temperature for one hour, and was determined to be complete by HPLC analysis. The mixture was treated with water (7.5 mL) and stirred for 1 minute, then acidified with 3M HCl (3027 μ L, 9.08 mmol) to pH 5.5-6. The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts were concentrated *in vacuo* to give a yellow viscous oil, which completely solidified upon placing under high vacuum to afford the product (102 mg, 21.1% yield). ^1H NMR (CDCl_3) δ 8.02 (s, 1H), 7.94 (s, 1H), 3.98 (s, 3H), 3.82 (s, 2H)

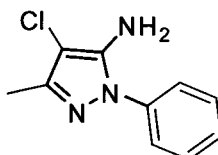
[00646] Step B: Preparation of 1,1'-dimethyl-1H,1'H-3,4'-bipyrazol-5-amine: Prepared by the method as described for Intermediate P1, substituting methyl hydrazine for ethyl 3-hydrazinylbenzoate hydrochloride and replacing 4,4-dimethyl-3-oxopentanenitrile with 3-(1-methyl-1H-pyrazol-4-yl)-3-oxopropanenitrile to yield the product as an ivory white solid (45 mg, 44.6% yield). MS (apci) $m/z = 178.1$ (M+H).

Intermediate P115**4-chloro-1,3-diphenyl-1H-pyrazol-5-amine**

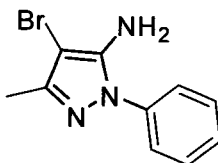
[00647] To a solution of 1,3-diphenyl-1H-pyrazol-5-amine (Table 1; 0.100 g, 0.425 mmol) in acetonitrile (2 mL) was added *N*-chlorosuccinimide (0.0568 g, 0.425 mmol). The pale yellow solution was stirred at ambient temperature for 3 hours, then concentrated *in vacuo* and purified by silica column chromatography eluting with 20% EtOAc/Hexanes to afford the product as a light brown oil (0.10 g, 87% yield). MS (apci) m/z = 270.0 (M+H).

Intermediate P116**4-bromo-1,3-diphenyl-1H-pyrazol-5-amine**

[00648] Prepared according to the procedure described for Intermediate P115, substituting *N*-chloro succinimide with *N*-bromo-succinimide. MS (apci) m/z = 313.9 (M+H).

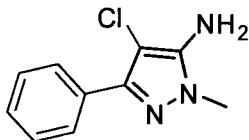
Intermediate P117**4-chloro-3-methyl-1-phenyl-1H-pyrazol-5-amine**

[00649] Prepared according to the procedure described for Intermediate P115, substituting 1,3-diphenyl-1H-pyrazol-5-amine with 3-methyl-1-phenyl-1H-pyrazol-5-amine. MS (apci) m/z = 207.9 (M+H).

Intermediate P118**4-bromo-3-methyl-1-phenyl-1H-pyrazol-5-amine**

[00650] Prepared according to the procedure described for Intermediate P117, substituting *N*-chloro succinimide with *N*-bromo-succinimide. MS (apci) m/z = 251.9 (M+H).

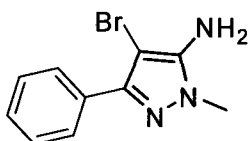
Intermediate P119



4-chloro-1-methyl-3-phenyl-1H-pyrazol-5-amine

[00651] Prepared according to the procedure described for Intermediate P115, substituting 1,3-diphenyl-1H-pyrazol-5-amine with 1-methyl-3-phenyl-1H-pyrazol-5-amine (Table 1). MS (apci) m/z = 208.0 (M+H).

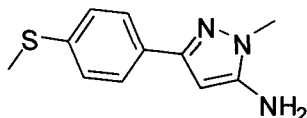
Intermediate P120



4-bromo-1-methyl-3-phenyl-1H-pyrazol-5-amine

[00652] Prepared according to the procedure described for Intermediate P119, substituting N-chloro succinimide with N-bromo-succinimide. MS (apci) m/z = 251.9 (M+H).

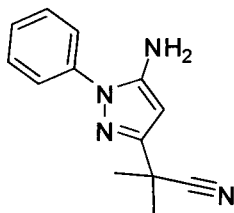
Intermediate P121



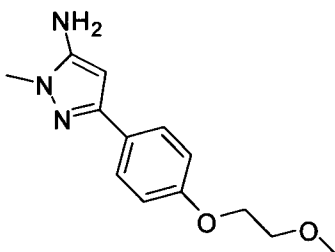
1-methyl-3-(4-(methylthio)phenyl)-1H-pyrazol-5-amine

[00653] Step A: Preparation of 3-(4-(methylthio)phenyl)-3-oxopropanenitrile: To a suspension of NaH (60% in mineral oil) (154 mg, 3.84 mmol) in dioxane (25.0 mL, 2.74 mmol) was added acetonitrile (0.217 mL, 4.12 mmol). The reaction mixture was stirred at ambient temperature for 30 minutes, then treated with methyl 4-(methylthio)benzoate (500 mg, 2.74 mmol) and heated to reflux for 15 hours. The suspension was cooled, then diluted with water (25 mL) and washed with Et₂O (25 mL). The aqueous layer was neutralized with 2M HCl (1.8 mL) and extracted with Et₂O (2 x 25 mL). The combined organic phases were washed with brine (25 mL), dried with MgSO₄, filtered and concentrated *in vacuo*. The resultant residue was purified by silica column chromatography eluting with 0-5% MeOH/DCM to afford the product (317 mg, 60.4% yield). ¹H NMR (CDCl₃) δ 7.82 (d, 2H), 7.30 (d, 2H), 4.02 (s, 2H), 2.54 (s, 3H).

[00654] Step B: Preparation of 1-methyl-3-(4-(methylthio)phenyl)-1H-pyrazol-5-amine: Prepared by the method as described in Intermediate P1, substituting methylhydrazine for ethyl 3-hydrazinylbenzoate hydrochloride and substituting 3-(4-(methylthio)phenyl)-3-oxopropanenitrile for 4,4-dimethyl-3-oxopentanenitrile to yield the product as a yellow solid (0.307 g, 96.7% yield). MS (apci) m/z = 220.0 (M+H).

Intermediate P1222-(5-amino-1-phenyl-1H-pyrazol-3-yl)-2-methylpropanenitrile

[00655] Prepared according to the procedure for Intermediate P121, substituting methyl 4-(methylthio)benzoate with ethyl 2-cyano-2-methylpropanoate in Step A and phenyl hydrazine hydrochloride for methyl hydrazine in Step B. MS (apci) $m/z = 227.1$ (M+H).

Intermediate P1233-(4-(2-methoxyethoxy)phenyl)-1-methyl-1H-pyrazol-5-amine

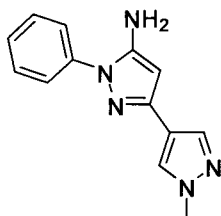
[00656] Step A: Preparation of 3-(4-(benzyloxy)phenyl)-3-oxopropanenitrile: Prepared according to the procedure described for Intermediate P121, substituting methyl 4-(methylthio)benzoate with methyl 4-(benzyloxy)benzoate in Step A. ^1H NMR (CDCl_3) δ 7.90 (d, 2H), 7.42 (m, 4H), 7.37 (m, 1H), 7.05 (d, 2H), 5.16 (s, 2H), 4.00 (s, 2H).

[00657] Step B: Preparation of 3-(4-(benzyloxy)phenyl)-1-methyl-1H-pyrazol-5-amine: Prepared by the method as described for Intermediate P1, substituting methylhydrazine for ethyl 3-hydrazinylbenzoate hydrochloride and 3-(4-(benzyloxy)phenyl)-3-oxopropanenitrile for 4,4-dimethyl-3-oxopentanenitrile to yield the product as a yellow solid. MS (apci) $m/z = 280.1$ (M+H).

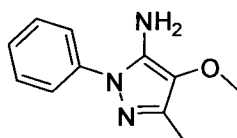
[00658] Step C: Preparation of 4-(5-amino-1-methyl-1H-pyrazol-3-yl)phenol: To a solution of 3-(4-(benzyloxy)phenyl)-1-methyl-1H-pyrazol-5-amine (47 mg, 0.17 mmol) in EtOH (5.0 mL) was added 5% Pd/C (9.0 mg, 0.0084 mmol) and stirred under a H_2 balloon for 17 hours. The reaction mixture was filtered through Celite®, rinsed with EtOH and concentrated in vacuo to afford the product (28 mg, 88% yield). MS (apci) $m/z = 190.1$ (M+H).

[00659] Step D: Preparation of 3-(4-(2-methoxyethoxy)phenyl)-1-methyl-1H-pyrazol-5-amine: To a solution of 4-(5-amino-1-methyl-1H-pyrazol-3-yl)phenol (14 mg, 0.074 mmol) in DMSO (0.50 mL, 7.0 mmol) was added Cs_2CO_3 (48 mg, 0.15 mmol) and 1-bromo-2-methoxyethane (9.7 μL , 0.10 mmol). The reaction mixture was stirred for 16 hours, then diluted

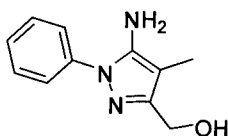
with water (10 mL) and extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried with MgSO_4 , filtered and concentrated to afford the crude product (22 mg, 120% yield). The crude product was used without purification in subsequent steps. MS (apci) $m/z = 248.0$ (M+H).

Intermediate P1241'-methyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-amine

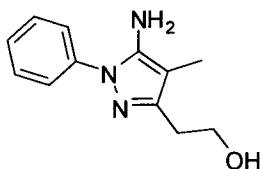
[00660] Prepared according to the procedure described for Intermediate P114, substituting methylhydrazine with phenylhydrazine in Step B. MS (apci) $m/z = 240.0$ (M+H).

Intermediate P1254-methoxy-3-methyl-1-phenyl-1H-pyrazol-5-amine

[00661] Prepared according to the procedure for Intermediate P121, substituting methyl 4-(methylthio)benzoate with ethyl acetate and substituting acetonitrile with 2-methoxyacetonitrile in Step A and phenyl hydrazine hydrochloride for methyl hydrazine in Step B. MS (apci) $m/z = 204.0$ (M+H).

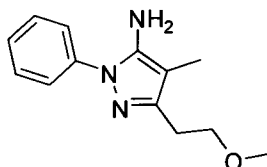
Intermediate P126(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)methanol

[00662] Prepared according to the procedure for Intermediate P112, substituting methyl 3-hydroxy-2,2-dimethylpropanoate with ethyl 2-hydroxyacetate in Step A. MS (apci) $m/z = 204.1$ (M+H).

Intermediate P1272-(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)ethanol

[00663] Prepared according to the procedure for Intermediate P112, substituting methyl 3-hydroxy-2,2-dimethylpropanoate with methyl 3-hydroxypropanoate in Step A. MS (apci) m/z = 218.0 (M+H).

Intermediate P128

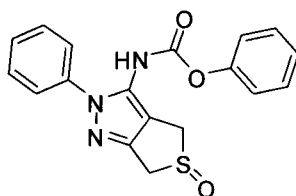


3-(2-methoxyethyl)-4-methyl-1-phenyl-1H-pyrazol-5-amine

[00664] Step A: Preparation of 5-methoxy-2-methyl-3-oxopentanenitrile: To a suspension of NaNH₂ (50 wt% suspension in toluene) (330 mg, 4.23 mmol) in THF (25 mL, 4.23 mmol) under N₂ at -78 °C was added propiononitrile (0.448 mL, 6.35 mmol), and the reaction mixture was stirred for 30 minutes. Methyl 3-methoxypropanoate (0.495 mL, 4.23 mmol) was added and the reaction mixture was stirred at -78 °C for 1 hour, then at 0 °C for 2.5 hours. The reaction mixture was diluted with H₂O (25 mL) and washed with Et₂O (25 mL). The basic aqueous phase was neutralized with 2M HCl (1.6 mL), then extracted with Et₂O (3 x 25 mL). The combined organic phases were washed with brine (25 mL), dried with MgSO₄, filtered, and concentrated to afford the crude product as a pale greenish oil (171 mg). The crude mixture was taken directly to the next step.

[00665] Step B: Preparation of 3-(2-methoxyethyl)-4-methyl-1-phenyl-1H-pyrazol-5-amine: Prepared by the method as described for Intermediate P1, substituting 5-methoxy-2-methyl-3-oxopentanenitrile for 4,4-dimethyl-3-oxopentanenitrile and substituting phenylhydrazine hydrochloride for ethyl 3-hydrazinylbenzoate hydrochloride to yield the product as a yellow solid (56 mg, 20% yield). MS (apci) m/z = 232.0 (M+H).

Intermediate P129

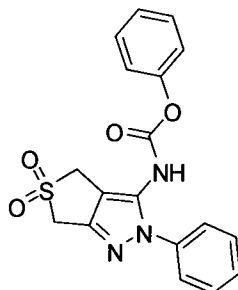


Phenyl (5-oxido-2-phenyl-4,6-dihydro-2H-thieno[3,4-c]pyrazol-3-yl)carbamate

[00666] A THF (4 mL) solution of phenyl 2-phenyl-4,6-dihydro-2H-thieno[3,4-c]pyrazol-3-ylcarbamate (Intermediate P130, Step B; 50 mg, 0.15 mmol) was cooled to -50 °C with an external dry-ice/MeCN bath and treated with a THF (2 mL) solution of 3-chlorobenzoperoxoic acid (33 mg, 0.13 mmol). After stirring for 1 hour, the mixture was quenched with Na₂S₂O₃ and water, extracted with EtOAc, washed with NaHCO₃ and brine, dried with MgSO₄, filtered, and

concentrated to give the product which was directly used in next step without further purification. MS (apci) $m/z = 354.1$ (M+H).

Intermediate P130



Phenyl (5,5-dioxido-2-phenyl-4,6-dihydro-2H-thieno[3,4-c]pyrazol-3-yl)carbamate

[00667] Step A: Preparation of 2-phenyl-4,6-dihydro-2H-thieno[3,4-c]pyrazol-3-amine:

A suspension of 4-oxotetrahydrothiophene-3-carbonitrile (1.00 g, 7.86 mmol) and phenylhydrazine hydrochloride (1.25 g, 8.65 mmol) in absolute EtOH (40 mL) was refluxed for 2 hours. After removal of solvent under reduced pressure, the white solid residue was triturated with 1 N NaOH (40 mL). The solid was collected by filtration, washed with 0.1 N NaOH, water, and hexanes (approx. 10 mL each) then dried on high vacuum to yield the product as white solid (1.6 g, 95% yield). MS (apci pos) $m/z = 218.1$ (M+H).

[00668] Step B: Preparation of phenyl 2-phenyl-4,6-dihydro-2H-thieno[3,4-c]pyrazol-3-ylcarbamate.

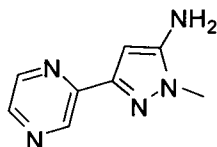
To a suspension of 2-phenyl-4,6-dihydro-2H-thieno[3,4-c]pyrazol-3-amine (500 mg, 2.30 mmol) in EtOAc (10 mL) was added NaOH (2M aq, 2.3 mL, 4.60 mmol), followed by dropwise addition of phenyl carbonochloridate (0.400 mL, 3.22 mmol). After stirring at ambient temperature for 2 hours, another portion of phenyl carbonochloridate (0.16 mL, 1.3 mmol) was added dropwise, and the reaction was stirred at ambient temperature for 15 hours. The reaction mixture was diluted with EtOAc (20 mL) and phase-separated. The organic phase was washed with H₂O, brine (25 mL each), then dried with Na₂SO₄, filtered and concentrated. The crude material was purified by reverse-phase column chromatography, eluting with 5-70% acetonitrile/water to yield the product as white solid (0.5 g, 64% yield). MS (apci pos) $m/z = 338.1$ (M+H).

[00669] Step C: Preparation of phenyl (5,5-dioxido-2-phenyl-4,6-dihydro-2H-thieno[3,4-c]pyrazol-3-yl)carbamate.

To a turbid solution of phenyl 2-phenyl-4,6-dihydro-2H-thieno[3,4-c]pyrazol-3-ylcarbamate (50 mg, 0.15 mmol) in DCM (1.5 mL) at 0 °C was added MCPBA (91 mg, 0.37 mmol, 70-75% water complex), and the mixture was stirred at ambient temperature for 10 min. The mixture was then diluted with DCM (3 mL) and washed with saturated aqueous NaHCO₃ (3 × 2 mL) and saturated aqueous Na₂S₂O₃ (3 × 2 mL). The organic layer was dried

with MgSO_4 , filtered and concentrated under reduced pressure to yield the title product as light yellowish foamy solid (31 mg, 57% yield, 95% pure). MS (apci pos) $m/z = 371.0$ ($M+H$).

Intermediate P132

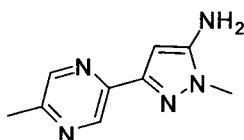


1-methyl-3-(pyrazin-2-yl)-1H-pyrazol-5-amine

[00670] Step A: Preparation of 3-oxo-3-(pyrazin-2-yl)propanenitrile: To a suspension of NaH (60% in mineral oil, 81.1 mg, 2.03 mmol) in dioxane (15 mL) was added acetonitrile (0.114 mL, 2.17 mmol), followed by methyl pyrazine-2-carboxylate (200 mg, 1.45 mmol) and the reaction heated to reflux for 2.5 hours. The reaction mixture was cooled to ambient temperature and diluted with H_2O (25 mL) and extracted with Et_2O (25 mL). The aqueous phase was neutralized with 2M aqueous HCl (0.7 mL), then extracted with 10% MeOH/DCM (3 x 25 mL). The combined organic phases were washed with brine (25 mL), dried with MgSO_4 , filtered, and concentrated to yield the crude product as an orange syrup (134 mg, 62.9% yield). ^1H NMR (CDCl_3) δ 9.32 (d, 1H), 8.87 (d, 1H), 8.68 (dd, 1H), 4.34 (s, 2H).

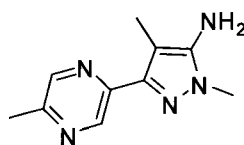
[00671] Step B: Preparation of 1-methyl-3-(pyrazin-2-yl)-1H-pyrazol-5-amine: To a suspension of 3-oxo-3-(pyrazin-2-yl)propanenitrile (67.0 mg, 0.455 mmol) in EtOH (5 mL) was added methylhydrazine (0.024 mL, 0.455 mmol). The reaction mixture was refluxed for 15 hours, then concentrated *in vacuo*. The crude product was purified by silica column chromatography, eluting with 0-5% MeOH/DCM to yield the product as a brown residue (33 mg, 41% yield). MS (apci) $m/z = 176.2$ ($M+H$).

Intermediate P133

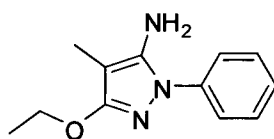


1-methyl-3-(5-methylpyrazin-2-yl)-1H-pyrazol-5-amine

[00672] Prepared by the method as described for Intermediate P107, substituting methyl isobutyrate in Step A with methyl 5-methylpyrazine-2-carboxylate and propionitrile with acetonitrile to afford 3-(5-methylpyrazin-2-yl)-3-oxopropanenitrile. In Step B, phenylhydrazine was replaced by methylhydrazine to afford the title pyrazole. MS (apci) $m/z = 190.2$ ($M+H$).

Intermediate P1341,4-dimethyl-3-(5-methylpyrazin-2-yl)-1H-pyrazol-5-amine

[00673] Prepared by the method as described for Intermediate P107, substituting methyl isobutyrate in Step A with methyl 5-methylpyrazine-2-carboxylate to afford 2-methyl-3-(5-methylpyrazin-2-yl)-3-oxopropanenitrile. In Step B, phenylhydrazine was replaced by methylhydrazine to afford the title compound. MS (apci) $m/z = 204.1$ (M+H).

Intermediate P1353-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-amine

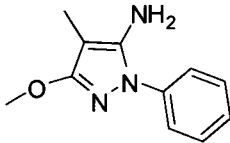
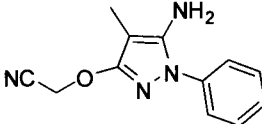
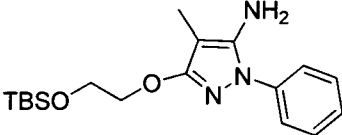
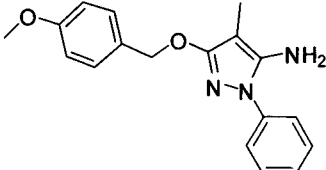
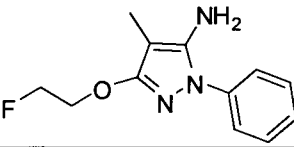
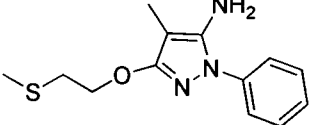
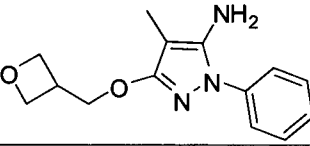
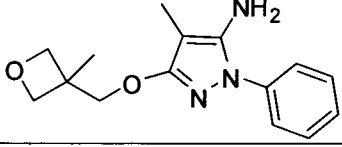
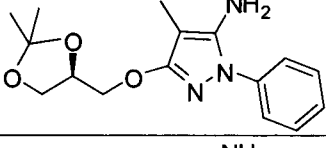
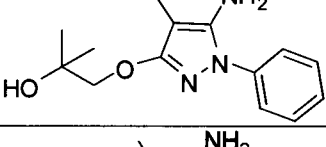
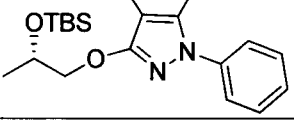
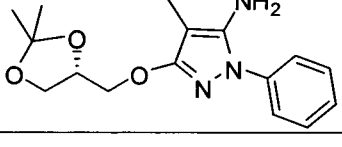
[00674] Step A: Preparation of 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one: A mixture of ethyl 2-cyanopropanoate (5.0 g, 46 mmol) and phenylhydrazine (5.9 g, 46 mmol) in dioxane (10 mL) was heated at 110 °C for 17 hours. The crude material was cooled to ambient temperature, concentrated, and triturated with cold EtOH and Et₂O. The resultant solid was filtered, washed with Et₂O, and dried under vacuum to give the product as a white solid (3.4 g, 39% yield). MS (apci) $m/z = 190.0$ (M-H).

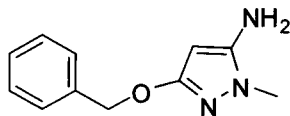
[00675] Step B: Preparation of 3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-amine: To a suspension of 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one (10.0 g, 52.9 mmol) in DMF (100 mL) was added K₂CO₃ (14.6 g, 106 mmol) and bromoethane (4.34 mL, 58.1) at ambient temperature. After stirring for 17 hours, the reaction mixture was treated with EtOAc and washed with water (3x, to obtain the *N*-alkylation product) and brine, dried with MgSO₄, filtered, and concentrated to give the product (5.35 g, 47% yield). MS (apci) $m/z = 218.1$ (M+H).

[00676] The compounds in Table 3 were prepared by the method as described for Intermediate P135, substituting bromoethane with the appropriate alkyl halide or alkyl methanesulfonate.

Table 3

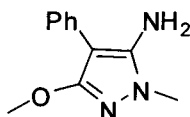
Intermediate #	Structure	Data
P200		MS (apci) $m/z = 248.1$ (M+H)

Intermediate #	Structure	Data
P201		MS (apci) m/z = 204.1 (M+H)
P202		MS (apci) m/z = 229.0 (M+H)
P203		MS (apci) m/z = 348.1 (M+H)
P204		MS (apci) m/z = 310.0 (M+H)
P205		MS (apci) m/z = 236.1 (M+H)
P206		MS (apci) m/z = 264.0 (M+H)
P207		MS (apci) m/z = 260.1 (M+H)
P208		MS (apci) m/z = 274.1 (M+H)
P209		MS (apci) m/z = 304.1 (M+H)
P210		MS (apci) m/z = 262.1 (M+H)
P211		MS (apci) m/z = 362.0 (M+H)
P212		MS (apci) m/z = 304.1 (M+H)

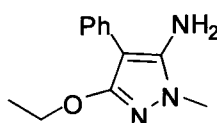
Intermediate P1363-(benzyloxy)-1-methyl-1H-pyrazol-5-amine

[00677] Step A: Preparation of 5-amino-1-methyl-4-phenyl-1H-pyrazol-3(2H)-one: To a suspension of ethyl 2-cyano-2-phenylacetate (2.56 g, 13.3 mmol) in EtOH (10 mL) was added dropwise methylhydrazine (1.09 mL, 19.9 mmol). The reaction was heated at 85 °C for 15 hours. The reaction mixture was cooled to 0 °C and filtered. The resultant solid was washed with cold EtOH (20 mL) and Et₂O (20 mL) to give the desired product (2.10 g, 83.7% yield). MS (apci) m/z = 190.2 (M+H)

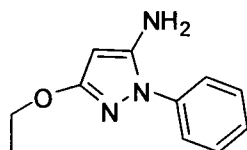
[00678] Step B: Preparation of 3-(benzyloxy)-1-methyl-1H-pyrazol-5-amine: A suspension of 5-amino-1-methyl-1H-pyrazol-3(2H)-one (0.35 g, 3.1 mmol), Benzyl chloride (0.43 g, 3.4 mmol), and K₂CO₃ (1.3 g, 9.3 mmol) in DMF (4 mL) was heated at 70 °C for 17 hours. After cooling, the reaction mixture was treated with EtOAc, washed with water and brine, dried with MgSO₄, and concentrated *in vacuo*. The crude product was purified by silica column chromatography eluting with 2-6% MeOH/DCM to afford the title compound (0.16 g, 25% yield). MS (apci) m/z = 204.0 (M+H).

Intermediate P1373-methoxy-1-methyl-4-phenyl-1H-pyrazol-5-amine

[00679] To a suspension of 5-amino-1-methyl-4-phenyl-1H-pyrazol-3(2H)-one (Step A of the preparation of Intermediate P136; 208 mg, 1.10 mmol) and K₂CO₃ (456 mg, 3.30 mmol) in DMF (5 mL) was added dropwise iodomethane (172 mg, 1.21 mmol). The reaction mixture was stirred for 15 hours. The solvent was removed under reduced pressure and the residue was purified by silica column chromatography eluting with 33% EtOAc/Hexanes to give the title pyrazole (66.0 mg, 30.4% yield). MS (apci) m/z = 204.1 (M+H).

Intermediate P1383-ethoxy-1-methyl-4-phenyl-1H-pyrazol-5-amine

[00680] Prepared as described in Intermediate P137, replacing iodomethane with iodoethane in Step B to afford the title compound. MS (apci) m/z = 218.2 (M+H).

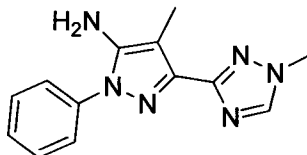
Intermediate P1393-ethoxy-1-phenyl-1H-pyrazol-5-amine

[00681] Prepared according to the procedure described for Intermediate 135, substituting ethyl-2-cyanopropanoate with ethyl-2-cyanoacetate in Step A. MS (apci) $m/z = 204.0$ (M+H).

[00682] The compounds in the following Table were prepared by the method as described for Intermediate P135, substituting bromoethane with the appropriate alkyl halide, alkyl methanesulfonate or epoxide.

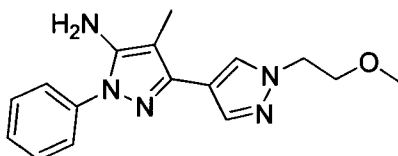
Intermediate #	Structure	MS (apci) m/z
P140		286.1 (M+H)
P141		303.1 (M+H)
P142		262.1 (M+H)
P143		402.2 (M+H)
P144		276.1 (M+H)
P145		363.1 (M+H)
P146		248.1 (M+H)
P147		248.1 (M+H)

Intermediate #	Structure	MS (apci) m/z
P148		302.1 (M+H)
P149		302.1 (M+H)
P150		262.1 (M+H)

Intermediate 1511'-(2-methoxyethyl)-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-amine

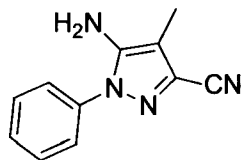
[00683] Step A: Preparation of methyl 1-methyl-1H-1,2,4-triazole-3-carboxylate: To a stirred suspension of NaH (60% oil dispersion, 0.346 g, 8.66 mmol) in DMF (20 mL) was added dropwise a solution of methyl 1H-1,2,4-triazole-3-carboxylate (1.00 g, 7.87 mmol) in DMF (20 mL) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 1 hour. MeI (0.982 mL, 15.7 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature overnight. The reaction was poured into cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried and concentrated. The residue was purified by column chromatography (3:1 hexanes/EtOAc) to give the title compound (0.380 g, 34% yield) as a white solid. MS (apci) m/z = 142.1 (M+H).

[00684] Step B: Preparation of 1'-(2-methoxyethyl)-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-amine: Prepared according to the method described for Intermediate P109, using methyl 1-methyl-1H-1,2,4-triazole-3-carboxylate as a replacement for methyl 2-methoxyacetate, and substituting propionitrile for acetonitrile in Step A. MS (apci) m/z = 255.1 (M+H).

Intermediate 1521'-(2-methoxyethyl)-4-methyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-amine

[00685] Prepared according to the method described for Intermediate P109, using ethyl 1-(2-methoxyethyl)-1*H*-pyrazole-4-carboxylate as a replacement for methyl 2-methoxyacetate, and substituting propionitrile for acetonitrile in Step A.

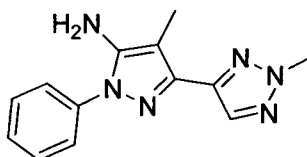
Intermediate 153



5-amino-4-methyl-1-phenyl-1*H*-pyrazole-3-carbonitrile

[00686] To a stirred solution of aniline (2.02 g, 21.7 mmol) in 6 N HCl (22 mL) was added dropwise a solution of NaNO₂ (1.50 g, 21.7 mmol) in water (20 mL) at 0-5 °C. The reaction mixture was stirred at 0 °C for 15 minutes. Acetic acid (10 mL) was added. This solution was added dropwise to a stirred solution of ethyl 2,3-dicyanobutanoate (Prepared according to the procedure described in *Bioorganic & Medicinal Chemistry*, **2004**, *12*, 3345 – 3356, 3.60 g, 21.7 mmol) in acetic acid (12 mL) and water (18 mL) at 0 °C. After stirring for 1 hour, concentrated ammonium hydroxide (50 mL) was added dropwise followed by THF (50 mL). The reaction was stirred at ambient temperature overnight. The organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried and concentrated. The residue was purified by flash chromatography on silica gel (3:1 hexanes/EtOAc) to give the title compound (2.95 g, 69% yield). MS (apci) *m/z* = 198.9 (M+H).

Intermediate 155



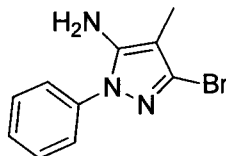
4-methyl-3-(2-methyl-2*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-5-amine

[00687] Step A: Preparation of ethyl 2-methyl-2*H*-1,2,3-triazole-4-carboxylate: A mixture of ethyl 2*H*-1,2,3-triazole-4-carboxylate (2.00 g, 14.2 mmol), K₂CO₃ (3.53 g, 25.5 mmol) and methyl iodide (3.54 mL, 56.7 mmol) in acetonitrile (40 mL) was stirred at 50 °C under nitrogen overnight. After cooling to ambient temperature, the mixture was filtered through Celite®. The filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (4:1 hexane/EtOAc) to give the title compound (0.780 g, 35% yield). MS (apci) *m/z* = 156.0 (M+H).

[00688] Step B: Preparation of 4-methyl-3-(2-methyl-2*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-5-amine: Prepared according to the method described for Intermediate P109 using ethyl

2-methyl-2*H*-1,2,3-triazole-4-carboxylate as a replacement for methyl 2-methoxyacetate, and substituting propionitrile for acetonitrile in Step A. MS (apci) $m/z = 254.9$ (M+H).

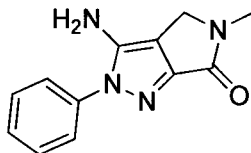
Intermediate 156



3-bromo-4-methyl-1-phenyl-1*H*-pyrazol-5-amine:

[00689] To a stirred solution of 5-amino-4-methyl-1-phenyl-1*H*-pyrazol-3(2*H*)-one (Intermediate P135, Step A, 1.00 g, 5.29 mmol) in MeCN (20 mL) was added POBr₃ (2.27 g, 7.93 mmol). The reaction mixture was heated at reflux for 3 hours. The reaction was concentrate *in vacuo*. The residue was taken up in DCM. Saturated aqueous NaHCO₃ solution was carefully added. The aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried and concentrated. The residue was purified by flash chromatography on silica gel (1:2 hexane/EtOAc to give the title compound (0.23g, 17% yield). MS (apci) $m/z = 251.8$ (M+H).

Intermediate 157



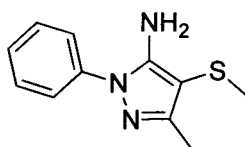
3-amino-5-methyl-2-phenyl-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(2*H*)-one

[00690] Step A: Preparation of ethyl 5-amino-4-((methylamino)methyl)-1-phenyl-1*H*-pyrazole-3-carboxylate: To a stirred solution of ethyl 5-amino-4-formyl-1-phenyl-1*H*-pyrazole-3-carboxylate (Prepared according to the procedure described in *J. Heterocyclic Chemistry*, **2010**, 47, p. 287-291, 142 mg, 0.548 mmol) in DCM (3 mL) was added 2.0 M MeNH₂ in THF (0.822 mL, 1.64 mmol). Two drops of acetic acid was added. The reaction mixture was stirred at ambient temperature overnight. MeOH (0.4 mL) was added followed by NaBH₄ (31 mg, 0.82 mmol) portionwise. The reaction was quenched by the slow addition of water. The mixture was extracted with DCM. The combined organic layers were washed with brine, dried and concentrated. The crude was used in the next step without further purification. MS (apci) $m/z = 275.0$ (M+H).

[00691] Step B: Preparation of 3-amino-5-methyl-2-phenyl-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(2*H*)-one: To a stirred solution of ethyl 5-amino-4-((methylamino)methyl)-1-phenyl-1*H*-pyrazole-3-carboxylate (crude, 65 mg, 0.24 mmol) in MeOH (0.5 mL) and THF (0.5 mL) was added 2 N NaOH (0.24 mL, 0.47 mmol). The reaction mixture was stirred at ambient

temperature for 4 hours and then concentrated *in vacuo*. To the residue was added water. The pH was adjusted to 4-5 using 1 N HCl. Water was evaporated under reduced pressure. The crude acid (58 mg) was dissolved in DMF (3 mL). Et₃N (66 μ L, 0.47 mmol) was added followed by EDCI (90 mg, 0.47 mmol) and HOBt (32 mg, 0.24 mmol). The reaction mixture was stirred at ambient temperature overnight and then partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried and concentrated. The residue was purified by flash chromatography on silica gel (2% MeOH in DCM) to give the title compound (15 mg, 28%) as a white solid. MS (apci) m/z = 228.9 (M+H).

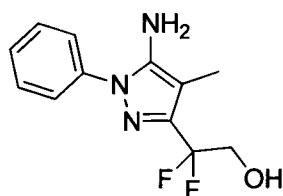
Intermediate 158



3-methyl-4-(methylthio)-1-phenyl-1H-pyrazol-5-amine

[00692] Prepared according to the method described for Intermediate P109, replacing methyl 2-methoxyacetate with ethyl acetate and replacing acetonitrile with 2-(methylthio)acetonitrile in Step A to afford the product as a brown oil. MS (apci) m/z = 220.1 (M+H).

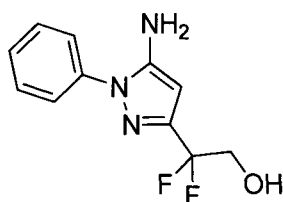
Intermediate 159



2-(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)-2,2-difluoroethanol

[00693] Prepared according to the method described for Intermediate P111, replacing acetonitrile with propionitrile and replacing methyl 3-hydroxy-2,2-dimethylpropanoate with ethyl 2,2-difluoro-3-hydroxypropanoate to afford the product as a pale yellow solid. MS (apci) m/z = 254.1 (M+H).

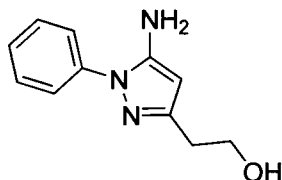
Intermediate 160



2-(5-amino-1-phenyl-1H-pyrazol-3-yl)-2,2-difluoroethanol

[00694] Prepared according to the method described for Intermediate P111, replacing methyl 3-hydroxy-2,2-dimethylpropanoate with ethyl 2,2-difluoro-3-hydroxypropanoate to afford the product as a pale yellow solid. MS (apci) $m/z = 240.0$ (M+H).

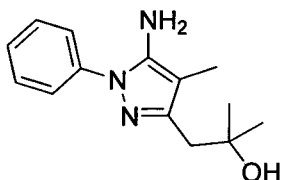
Intermediate 161



2-(5-amino-1-phenyl-1H-pyrazol-3-yl)ethanol

[00695] Prepared according to the method described in Intermediate P111, replacing methyl 3-hydroxy-2,2-dimethylpropanoate with methyl 3-hydroxypropanoate in Step A. MS (apci) $m/z = 204.1$ (M+H).

Intermediate 162



1-(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)-2-methylpropan-2-ol

[00696] Step A: Preparation of ethyl 3-hydroxy-3-methylbutanoate: To a solution of lithium bis(trimethylsilyl)amide (1M in THF) (100 mL, 100 mmol) in THF (100 mL) under N₂ and cooled to -78 °C was added ethyl acetate (9.74 mL, 100 mmol). The reaction mixture was stirred for 30 minutes, and then acetone (8.81 mL, 120 mmol) was added. The reaction mixture was stirred for 10 minutes, and then quenched with HCl (2M aqueous, 70 mL, 140 mmol) and allowed to warm to ambient temperature. The reaction mixture was extracted with EtOAc (2 x 150 mL). The organic phases were combined and washed with saturated aqueous NaHCO₃ (2 x 50 mL), dried (MgSO₄), filtered and concentrated to afford the product as a yellow oil (12.8 g, 88% yield). ¹H NMR (CDCl₃) δ 4.18 (q, 3H), 2.49 (s, 2H), 1.29 (m, 9H).

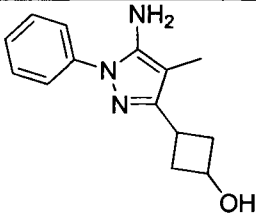
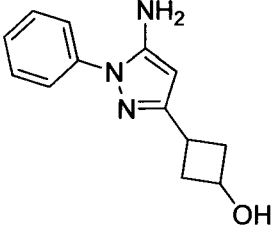
[00697] Step B: Preparation of 5-hydroxy-5-methyl-3-oxohexanenitrile: To a solution of propionitrile (1.77 mL, 30.5 mmol) in THF (100 mL) under N₂ at -78 °C was added lithium bis(trimethylsilyl)amide (1M in THF) (27.9 mL, 27.9 mmol). Stirred 1 hour, then ethyl 3-hydroxy-3-methylbutanoate (1.86 g, 12.7 mmol) was added. The reaction mixture was stirred at -78 °C for 1 hour, then stirred at 0 °C for 1.5 hours, then diluted with H₂O (100 mL) and extracted with Et₂O (50 mL). The phases were separated and the basic aqueous phase was neutralized with HCl (6M aqueous, 4.5 mL), then extracted with Et₂O (3 x 75 mL). The combined organic phases were washed with brine (75 mL), dried (MgSO₄), filtered, and

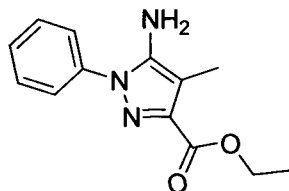
concentrated to afford the product as a pale yellow oil (1.24 g, 63% yield). ^1H NMR (CDCl_3) δ 3.54 (m, 1H), 2.89 (s, 2H), 1.50 (d, 3H), 1.32 (s, 3H), 1.31 (s, 3H).

[00698] Step C: Preparation of 1-(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)-2-methylpropan-2-ol: To a suspension of phenylhydrazine (0.793 mL, 7.99 mmol) and HCl (5-6M in iPrOH, 1.60 mL, 7.99 mmol) in EtOH (25 mL) was added a solution of 5-hydroxy-2,5-dimethyl-3-oxohexanenitrile (1.24 g, 7.99 mmol) in EtOH (25 mL). The reaction mixture was refluxed for 17 hours, then cooled to ambient temperature, diluted with saturated aqueous NaHCO_3 (10 mL), extracted 10:90 MeOH/DCM (3 x 25 mL), and the combined organic phases were dried (MgSO_4), filtered and concentrated. Purified by silica column chromatography eluting with 0-75% acetone/hexanes to afford the title compound as an orange oil (1.13 g, 58% yield). MS (apci) m/z = 246.1 (M+H).

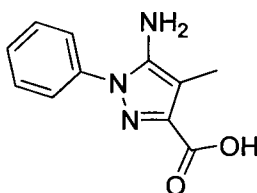
[00699] The following pyrazole intermediates were prepared according to the method used for the preparation of Intermediate 162, Steps B and C, using the appropriate starting material. For the preparation of Intermediates 168 and 169, the starting material (purchased from Oakwood) was a mixture of cis and trans diastereomers.

Intermediate #	Structure	Name	MS (apci) m/z
163		1-(5-amino-1-phenyl-1H-pyrazol-3-yl)-2-methylpropan-2-ol	232.1 (M+H)
164		(S)-1-(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)propan-2-ol	232.1 (M+H)
165		(S)-1-(5-amino-1-phenyl-1H-pyrazol-3-yl)propan-2-ol	218.1 (M+H)
166		(R)-1-(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)propan-2-ol	232.1 (M+H)
167		(R)-1-(5-amino-1-phenyl-1H-pyrazol-3-yl)propan-2-ol	218.1 (M+H)

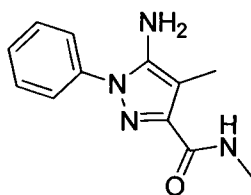
Intermediate #	Structure	Name	MS (apci) m/z
168		3-(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)cyclobutanol	244.1 (M+H)
169		3-(5-amino-1-phenyl-1H-pyrazol-3-yl)cyclobutanol	230.1 (M+H)

Intermediate 170ethyl 5-amino-4-methyl-1-phenyl-1H-pyrazole-3-carboxylate

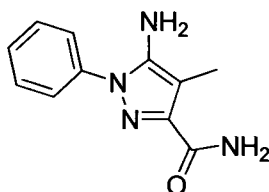
[00700] Prepared according to the method described for Intermediate P109, replacing methyl 2-methoxyacetate with diethyl oxalate and replacing acetonitrile with propionitrile in Step A to afford the product as a yellow solid. MS (apci) m/z = 246.1 (M+H).

Intermediate 1715-amino-4-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid

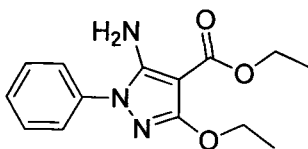
[00701] To a solution of ethyl 5-amino-4-methyl-1-phenyl-1H-pyrazole-3-carboxylate (Intermediate 170, 1.52 mg, 6.21 mmol) in THF (12 mL) and MeOH (6 mL) was added LiOH (2M aq, 9.31 mL, 18.6 mmol). The reaction mixture was stirred at ambient temperature for 19 hours, then partially concentrated under reduced pressure, then neutralized with 6M HCl (3.2 mL), extracted with 10:90 MeOH/DCM (3 x 25 mL), and the combined organic extracts were washed with brine (50 mL), dried (MgSO₄), filtered and concentrated to give the title compound as a yellow solid (1.3 g, 96% yield) MS (apci) m/z = 218.1 (M+H).

Intermediate 1725-amino-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide

[00702] To a solution of 5-amino-4-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid (Intermediate 171, 223 mg, 1.02 mmol) in acetonitrile (10 mL) were added DIEA (0.71 mL, 4.10 mmol), methanamine hydrochloride (138 mg, 2.05 mmol), DMF (2 mL), and then HATU (428 mg, 1.13 mmol). The reaction mixture was stirred at ambient temperature for 19 hours and then partially concentrated under reduced pressure. The mixture was purified by reverse-phase column chromatography, eluting with 5-60% acetonitrile/water to afford the title compound as a pale yellow solid (182 mg, 77% yield). MS (apci) m/z = 231.1 (M+H).

Intermediate 1735-amino-4-methyl-1-phenyl-1H-pyrazole-3-carboxamide

[00703] A solution of 5-amino-4-methyl-1-phenyl-1H-pyrazole-3-carbonitrile (150 mg, 0.757 mmol) in concentrated H₂SO₄ (0.5 mL) was stirred at ambient temperature for 17 hours. The reaction mixture was cooled and neutralized by the addition of aqueous NaOH (2M, 11 mL), then extracted 10% MeOH/DCM (5 x 10 mL), and the combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated under reduced pressure to afford the title compound as a white solid (151 mg, 95% yield). MS (apci) m/z = 239.1 (M+Na).

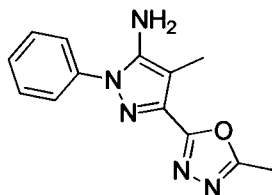
Intermediate 174ethyl 5-amino-3-ethoxy-1-phenyl-1H-pyrazole-4-carboxylate

[00704] Step A: Preparation of diethyl 2-cyanomalonate: To a suspension of NaH (60 wt% in mineral oil, 499 mg, 12.49 mmol) in THF (100 mL) under N₂ at 0 °C was added diethyl malonate (1.90 mL, 12.49 mmol). The ice bath was removed and the reaction mixture was stirred at ambient temperature for 30 minutes, then cooled to 0 °C and cyanic bromide (5M in

MeCN, 2.5 mL, 12.49 mmol) was added. The reaction mixture was stirred at ambient temperature for 19 hours, then diluted with H₂O (50 mL), extracted with Et₂O (50 mL). The aqueous phase was neutralized with HCl (2M aq, 3 mL) then extracted with DCM (2 x 50 mL). The combined DCM extracts were dried (MgSO₄), filtered, and concentrated to afford the product as a yellow oil (837 mg, 36% yield). ¹H NMR (CDCl₃) δ 4.46 (s, 1H), 4.35 (q, 4H), 1.35 (t, 6H).

[00705] Step B: Preparation of ethyl 5-amino-3-ethoxy-1-phenyl-1H-pyrazole-4-carboxylate: Prepared according to the method described for Intermediate P135, replacing ethyl 2-cyanopropanoate with diethyl 2-cyanomalonate in Step A to afford the product as a brown syrup (400 mg, 32% yield). MS (apci) m/z = 276.1 (M+H).

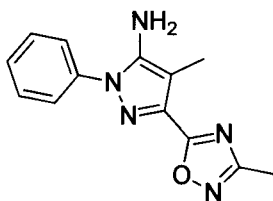
Intermediate 175



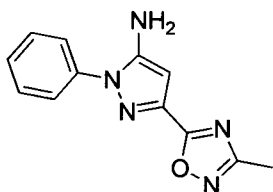
4-methyl-3-(5-methyl-1,3,4-oxadiazol-2-yl)-1-phenyl-1H-pyrazol-5-amine

[00706] Step A: Preparation of N'-acetyl-5-amino-4-methyl-1-phenyl-1H-pyrazole-3-carbohydrazide: To a solution of 5-amino-4-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid (Intermediate 171, 93 mg, 0.428 mmol) in DCM (5 mL) and DIEA (0.149 mL, 0.856 mmol) was added isobutyl carbonochloridate (0.061 mL, 0.471 mmol). The reaction mixture was stirred at ambient temperature for 1 hour, then acetohydrazide (48 mg, 0.642 mmol) was added. The reaction mixture was stirred at ambient temperature for 18 hours, then diluted with H₂O (10 mL), extracted DCM (2 x 10 mL), dried (MgSO₄), filtered and concentrated under reduced pressure to afford the product as a pale yellow solid (119 mg, 101% yield). MS (apci) m/z = 274.1 (M+H).

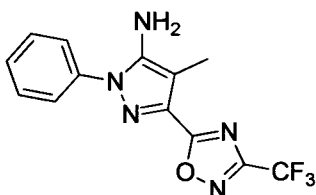
[00707] Step B: Preparation of 4-methyl-3-(5-methyl-1,3,4-oxadiazol-2-yl)-1-phenyl-1H-pyrazol-5-amine: A mixture of N'-acetyl-5-amino-4-methyl-1-phenyl-1H-pyrazole-3-carbohydrazide (117 mg, 0.428 mmol) and POCl₃ (0.5 mL) was heated in a pressure tube to 90 °C for 1 hour. The reaction mixture was transferred to a separatory funnel with EtOAc (5 mL), then diluted with saturated aqueous NaHCO₃ (20 mL), extracted with EtOAc (2 x 15 mL), dried (MgSO₄), filtered and concentrated. The residue was purified by silica column chromatography eluting with 0-75% acetone/hexanes to afford the title compound as a yellow solid (19.6 mg, 18% yield). MS (apci) m/z = 256.1 (M+H).

Intermediate 176**4-methyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1-phenyl-1H-pyrazol-5-amine**

[00708] To a suspension of NaH (60% in mineral oil, 36 mg, 0.897 mmol) in THF (5 mL) under N₂ was added N-hydroxyacetimidamide (66 mg, 0.897 mmol). The reaction mixture was heated to reflux for 1 hour, then cooled to ambient temperature and ethyl 5-amino-4-methyl-1-phenyl-1H-pyrazole-3-carboxylate (Intermediate 170, 200 mg, 0.815 mmol) was added. The reaction mixture was heated to reflux for 18 hours, then cooled to ambient temperature and additional NaH (60% in mineral oil, 18 mg, 0.449 mmol) was added. The reaction mixture was heated to reflux for 4 hours, then diluted with H₂O (10 mL), extracted DCM (2 x 15 mL), and the combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography eluting with 0-50% acetone/hexanes to afford the title compound as an orange solid (84 mg, 40% yield). MS (apci) m/z = 256.1 (M+H).

Intermediate 177**3-(3-methyl-1,2,4-oxadiazol-5-yl)-1-phenyl-1H-pyrazol-5-amine**

[00709] Prepared according to the method described in Intermediate 176, replacing ethyl 5-amino-4-methyl-1-phenyl-1H-pyrazole-3-carboxylate with ethyl 5-amino-1-phenyl-1H-pyrazole-3-carboxylate (Nanjing Chemlin Chemical Co.) to afford the product as a tan solid (83 mg, 53% yield). MS (apci) m/z = 242.1 (M+H).

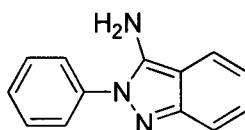
Intermediate 178**4-methyl-1-phenyl-3-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-5-amine**

[00710] Step A: Preparation of 2,2,2-trifluoro-N'-hydroxyacetimidamide: To a suspension of hydroxylamine hydrochloride (5.45 g, 78.4 mmol) in MeOH (100 mL) was added

NaOMe (25 wt % solution in MeOH, 17.9 mL, 78.4 mmol) and the mixture stirred at ambient temperature for 10 minutes, then filtered and the solid was washed with MeOH. The filtrate was cooled to 0 °C and then 2,2,2-trifluoroacetonitrile (7.45 g, 78.4 mmol) gas was bubbled into the solution over 30 minutes. The reaction mixture was then allowed to warm to ambient temperature for 19 hours. The solution was concentrated under reduced pressure to 50 mL and the solids were filtered. The filtrate was concentrated, re-suspended in cold MeOH, and filtered. The filtrate was concentrated, again re-suspended in cold MeOH, and filtered. The filtrate was concentrated to give the product as a waxy white solid (6.7 g, 67% yield). ^1H NMR (CD_3CN) δ 8.32 (s, 1H), 5.25 (br s, 2H). ^{19}F NMR (CD_3CN) δ -71.8 (s).

[00711] Step B: Preparation of 4-methyl-1-phenyl-3-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-5-amine: To a suspension of NaH (60% in mineral oil, 356 mg, 0.897 mmol) in THF (5 mL, 0.815 mmol) under N_2 was added 2,2,2-trifluoro-N'-hydroxyacetimidamide (115 mg, 0.897 mmol). The reaction mixture was heated to reflux for 1 hour, then cooled to ambient temperature and powdered 4A molecular sieves (200 mg) and ethyl 5-amino-4-methyl-1-phenyl-1H-pyrazole-3-carboxylate (Intermediate 170; 200 mg, 0.815 mmol) were added and heated to reflux. The reaction mixture was heated to reflux for 18 hours, then filtered, diluted with H_2O (15 mL), extracted DCM (2 x 25 mL), and the combined organic extracts were washed with brine (25 mL), dried (MgSO_4), filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography eluting with 0-50% acetone/hexanes to afford the title compound as a white solid (44 mg, 17% yield). MS (apci) m/z = 310.1 ($\text{M}+\text{H}$).

Intermediate 179



2-phenyl-2H-indazol-3-amine

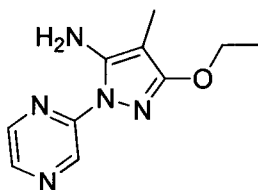
[00712] Step A: Preparation of 1-(2-iodophenyl)-2-phenyldiazene: To a solution of 2-iodoaniline (1.00 g, 4.57 mmol) in acetic acid (46 mL) was added nitrosobenzene (0.880 g, 8.22 mmol) and the mixture was heated at 85 °C for 16 hours. The mixture was cooled to ambient temperature, poured into water and slowly treated with saturated NaHCO_3 until basic. The mixture was extracted with EtOAc (3X) and the combined extracts were washed with water, saturated NaCl and dried over MgSO_4 . The solution was filtered, concentrated and the residue purified by reverse phase chromatography to provide the title compound as a red solid (0.880 g,

63% yield). ^1H NMR (CDCl_3) δ 7.23-7.39 (m, 3H), 7.64 (d, 1H), 7.56-7.51 (m, 3H), 7.45 (t, 1H), 7.1 (t, 1H).

[00713] Step B: 2-(phenyldiazenyl)benzonitrile: To a solution of 1-(2-iodophenyl)-2-phenyldiazene (0.44 g, 1.4 mmol) in 1-propanol (14 mL) was added CuCN (0.900 g, 10.0 mmol) and the reaction was heated at reflux for 16 hours. The mixture was cooled to ambient temperature, filtered and the collected solid washed with CH_2Cl_2 . The combined filtrate and washes were concentrated to provide the title compound as red-orange solid that was dried in vacuum (0.280 g, 95% yield). ^1H NMR (CDCl_3) δ 8.03-8.06 (m, 2H), 7.88 (dd, 2H), 7.71 (t, 1H), 7.54-7.58 (m, 4H).

[00714] Step C: 2-phenyl-2H-indazol-3-amine: A mixture of 2-(phenyldiazenyl)benzonitrile (0.28 g, 1.35 mmol) and SnCl_2 dihydrate (0.562 mL, 6.76 mmol) in EtOH (14 mL) was heated at reflux for 16 hours. The mixture was cooled to ambient temperature and concentrated. The residue was diluted with EtOAc and water and filtered. The aqueous layer was removed and the EtOAc layer was washed with water. The combined aqueous fractions were basified with saturated NaHCO_3 and extracted with CH_2Cl_2 (2X). The combined organic layers were dried over MgSO_4 , filtered and concentrated to provide the title compound as a light purple solid that was dried in vacuum (0.241 g, 85% yield). ^1H NMR (CDCl_3) δ 7.69 (d, 2H), 7.52-7.58 (m, 3H), 7.47 (d, 2H), 7.26 (t, 1H), 6.90 (t, 1H), 4.28 (br s, 2H).

Intermediate 180

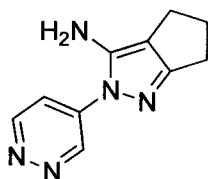


3-ethoxy-4-methyl-1-(pyrazin-2-yl)-1H-pyrazol-5-amine

[00715] Step A: 5-amino-4-methyl-1-(pyrazin-2-yl)-1H-pyrazol-3(2H)-one: To a mixture of 2-hydrazinylpyrazine (0.551 g, 5.00 mmol) and ethyl 2-cyanopropanoate (0.669 g, 5.00 mmol) in abs. EtOH (10 mL) was added 3M NaOEt in EtOH (0.167 mL, 0.501 mmol) and the mixture was heated at reflux for 64 hours. The mixture was concentrated and the residual yellow-brown solid was treated with EtOAc (30 mL) and sonicated. The resulting tan suspension was stirred vigorously for 8 hours. The solid was collected via vacuum filtration, washed with EtOAc and dried in vacuum to afford the title compound as a light tan powder (682 mg, 71%). ^1H NMR ($\text{DMSO}-d_6$) δ 10.3 (br s, 1H), 8.82 (s, 1H), 8.30 (d, 2H), 6.55 (s, 2H), 1.71 (s, 3H).

[00716] Step B: 3-ethoxy-4-methyl-1-(pyrazin-2-yl)-1H-pyrazol-5-amine: A mixture of 5-amino-4-methyl-1-(pyrazin-2-yl)-1H-pyrazol-3(2H)-one (382 mg, 2.00 mmol) and powdered K_2CO_3 (552 mg, 4.00 mmol) in dry DMF (3.0 mL) was stirred at ambient temperature for 10 minutes. The mixture was cooled to 0 °C and bromoethane (229 mg, 2.10 mmol) was added. The mixture was allowed to reach ambient temperature and was stirred 24 hours. The reaction mixture poured into cold H_2O (12 mL), allowed to reach ambient temperature and was extracted with EtOAc (3X). The combined extracts were washed with saturated NaCl (2X), dried over $MgSO_4$ and activated carbon. The dried solution was diluted with an equal volume of hexanes and filtered through a SiO_2 plug capped with a $MgSO_4$ layer eluting with 50% EtOAc-hexanes. The filtrate was concentrated and the residual yellow solid was washed with hexanes (3X) and dried in vacuum to afford the title compound as a light yellow crystalline solid (195 mg, 45%). 1H NMR ($CDCl_3$) δ 9.10 (s, 1H), 8.23 (s, 1H), 8.14 (s, 1H), 5.50 (br s, 2H), 4.33 (q, 2H), 1.80 (s, 3H), 1.42 (t, 3H).

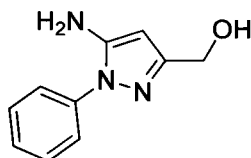
Intermediate 181



2-(pyridazin-4-yl)-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-amine

[00717] A suspension of 4-hydrazinylpyridazine hydrobromide (0.368 g, 1.93 mmol) in absolute EtOH (5 mL) was treated with 2-oxocyclopentanecarbonitrile (0.191 g, 1.75 mmol) and the mixture was heated at reflux for 22 hours. The mixture was cooled to ambient temperature and was concentrated to an orange solid. The solid was suspended in 1M NaOH and stirred for 10 minutes. The solid was collected, washed thoroughly with H_2O and Et_2O and dried in vacuum to furnish title compound as a tan powder (.323 g, 92%). MS (apci) m/z = 202.1 (M+H).

Intermediate 182



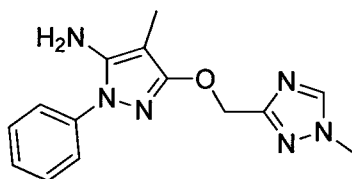
(5-amino-1-phenyl-1H-pyrazol-3-yl)methanol

[00718] Step A: Ethyl 2-(tert-butyldimethylsilyloxy)acetate: A mixture of ethyl 2-hydroxyacetate (3.00 g, 28.8 mmol), TBDMS-Cl (5.21 g, 34.6 mmol) and imidazole (2.55 g, 37.5 mmol) was stirred at ambient temperature for 60 hours. The mixture was concentrated and

the residue was purified by SiO₂ chromatography eluting with 10% EtOAc-hexanes to provide the title compound as a colorless oil (4.12 g, 65%). ¹H NMR (CDCl₃) δ 4.12 (s, 2H), 4.09 (q, 2H), 1.17 (t, 3H), 0.18 (s, 9H), 0.00 (s, 6H).

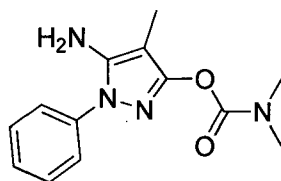
[00719] Step B: (5-amino-1-phenyl-1H-pyrazol-3-yl)methanol: A solution of acetonitrile (0.526 mL, 10.1 mmol) in dry THF (20.4 mL, 9.16 mmol) was cooled to -78 °C and 2.5M nBuLi in hexanes (4.21 mL, 10.5 mmol) was added dropwise. The reaction mixture was stirred for 15 minutes and ethyl 2-(tert-butyldimethylsilyloxy)acetate (2.00 g, 9.16 mmol) was added. The reaction mixture was allowed to warm to ambient temperature and was stirred for 2 hours. The reaction mixture was diluted with ice water and was concentrated. The residual aqueous mixture was acidified to pH=5 and extracted with EtOAc (3X). The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated. The residual brown oil was dissolved in MeOH (23 mL) and phenyl hydrazine (0.907 mL, 9.14 mmol) was added. The mixture was treated with concentrated HCl (3.81 mL, 45.7 mmol) and heated at reflux for 18 hours. Upon cooling, the mixture was concentrated and the residue was partitioned into H₂O and CH₂Cl₂. The mixture was filtered and the organic layer was removed from the filtrate. The aqueous portion was washed with CH₂Cl₂ and was treated with saturated NaHCO₃ until basic. The aqueous mixture was extracted with CH₂Cl₂ (3X) and the combined organic fractions were dried over MgSO₄, filtered and concentrated. The residue was purified by silica column chromatography using 70-100% EtOAc/hexanes gradient elution followed by 0-5% MeOH/EtOAc. The product pools were combined and concentrated to give the title compound as a yellow foam (0.760 g, 44% yield). MS (apci) m/z = 190.1 (M+H).

Intermediate 183

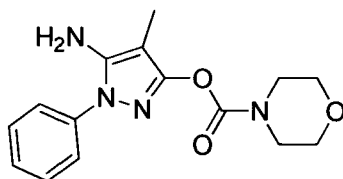


4-methyl-3-((1-methyl-1H-1,2,4-triazol-3-yl)methoxy)-1-phenyl-1H-pyrazol-5-amine

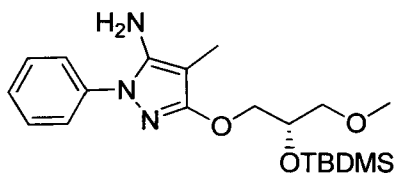
[00720] The title compound was prepared by the method as described for Intermediate P135, substituting bromoethane with 3-(chloromethyl)-1-methyl-1H-1,2,4-triazole hydrochloride. The product was isolated as a gold syrup (110 mg, 27%). MS (apci) m/z = 285.1 (M+H).

Intermediate 1845-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl dimethylcarbamate

[00721] A mixture of 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one (Intermediate P135 Step A, 0.378 g, 2.00 mmol) and powdered K_2CO_3 (0.553 g, 4.00 mmol) in dry DMF (4 mL) was stirred at ambient temperature for 5 minutes. Dimethylcarbamoyl chloride (0.206 mL, 2.20 mmol) was added and the mixture was stirred for 6 hours. The mixture was poured into chilled H_2O (40 mL) and was extracted with EtOAc (3X). The combined extracts were washed with saturated NaCl (2X), dried over $MgSO_4$ and filtered through a SiO_2 plug capped with a $MgSO_4$ layer (EtOAc elution). The filtrate was concentrated and the residue dried in vacuum to give the title compound as a light gold syrup (.507 g, 97%). MS (apci) m/z = 261.1 (M+H).

Intermediate 1855-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl morpholine-4-carboxylate

[00722] The title compound was prepared using morpholine-4-carbonyl chloride in the procedure outlined for 5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl dimethylcarbamate (Intermediate 184). The compound was isolated as a light yellow wax (0.285 g, 47%). 1H NMR ($CDCl_3$) δ 7.54 (d, 2H), 7.43 (t, 2H), 7.31 (t, 1H), 3.66-3.78 (m, 8H), 3.57 (br s, 2H), 1.85 (s, 3H).

Intermediate 186

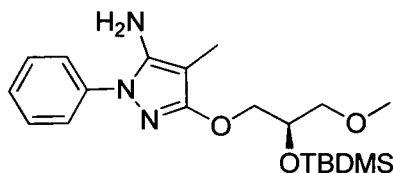
(S)-3-(2-(((tert-butyldimethylsilyl)oxy)-3-methoxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-amine

[00723] Step A: (S)-1-(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yloxy)-3-methoxypropan-2-ol: A mixture of 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one (P135 Step A, 1.21 g, 6.40 mmol) and powdered K_2CO_3 (1.77 g, 12.8 mmol) in dry DMF (12 mL) was stirred at ambient temperature for 10 minutes. (S)-2-(methoxymethyl)oxirane (0.622 mL, 6.72

mmol) was added and the mixture was stirred at 80 °C for 6 hours. The mixture was cooled to ambient temperature, poured into chilled H₂O (25 mL) and extracted with EtOAc (3X). The combined extracts were washed with saturated NaCl (2X), dried over MgSO₄ and filtered through a SiO₂ plug capped with a layer of MgSO₄ eluting with EtOAc. The filtrate was concentrated to give the title compound as a colorless, viscous oil (701 mg, 40%). MS (apci) $m/z = 278.1$ (M+H).

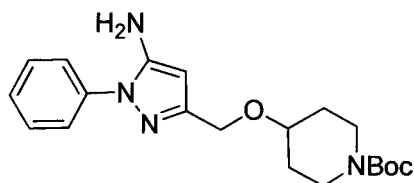
[00724] Step B: (S)-3-(2-((tert-butyldimethylsilyl)oxy)-3-methoxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-amine: To a solution of TBDMS-Cl (725 mg, 4.81 mmol) and imidazole (390 mg, 5.72 mmol) in dry DMF (7.0 mL) was added (S)-1-(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yloxy)-3-methoxypropan-2-ol (635 mg, 2.29 mmol) in dry DMF (2 mL). The mixture stirred at ambient temperature for 2.5 hours. The mixture added to H₂O (70 mL), mixed for 5 minutes and extracted with Et₂O (3X). The combined extracts were washed with saturated NaCl (2X) and dried over MgSO₄. The dried solution was filtered through a SiO₂ plug capped with a layer of MgSO₄ (Et₂O elution). The filtrate was concentrated to give the title compound as a colorless oil that was dried in vacuum (940 mg, 105%). MS (apci) $m/z = 392.2$ (M+H). ¹H NMR (CDCl₃) δ 7.50 (d, 2H), 7.40 (t, 2H), 7.23 (t, 1H), 4.09-4.30 (m, 3H), 3.57 (br s, 2H), 3.38-3.44 (m, 2H), 3.32 (s, 3H), 1.83 (s, 3H), 0.88 (s, 9H), 0.11 (s, 6H).

Intermediate 187



(R)-3-(2-((tert-butyldimethylsilyl)oxy)-3-methoxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-amine

[00725] The title compound was prepared using the procedure described for (S)-3-(2-((tert-butyldimethylsilyl)oxy)-3-methoxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-amine (Intermediate 186) substituting (S)-2-(methoxymethyl)oxirane with (R)-2-(methoxymethyl)oxirane in Step A. The product was obtained as a colorless syrup (921 mg, 38% over 2 steps). MS (apci) $m/z = 392.2$ (M+H). ¹H NMR (CDCl₃) δ 7.50 (d, 2H), 7.40 (t, 2H), 7.23 (t, 1H), 4.09-4.30 (m, 3H), 3.57 (br s, 2H), 3.38-3.44 (m, 2H), 3.32 (s, 3H), 1.83 (s, 3H), 0.88 (s, 9H), 0.11 (s, 6H).

Intermediate 188tert-butyl 4-((5-amino-1-phenyl-1H-pyrazol-3-yl)methoxy)piperidine-1-carboxylate

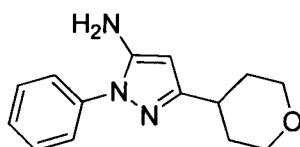
[00726] Step A: tert-butyl 4-(2-ethoxy-2-oxoethoxy)piperidine-1-carboxylate: A solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (2.00 g, 9.94 mmol) in dry THF (25 mL) was cooled to 0 °C and KOtBu (1.12 g, 9.94 mmol) was added. The mixture was allowed to reach ambient temperature and was stirred for 10 minutes. The mixture was cooled to 0 °C and ethyl 2-bromoacetate (1.65 mL, 14.9 mmol) was added dropwise. The reaction was allowed to reach ambient temperature and was stirred for 17 hours. The mixture was partitioned into in H₂O and EtOAc, mixed and the organic layer was removed. The organic layer was dried over MgSO₄, filtered and concentrated. The residual thick yellow oil was purified by silica chromatography using a 10-25% EtOAc/hexanes gradient elution to afford the title compound as a colorless oil (0.967 g, 34% yield). ¹H NMR (CDCl₃) δ 4.22 (q, 2H), 4.12 (s, 2H), 3.67-3.84 (m, 2H), 3.52-3.63 (m, 1H), 3.05-3.11 (m, 2H), 1.81-1.90 (m, 2H), 1.53-1.62 (m, 2H), 1.45 (s, 9H), 1.29 (t, 3H).

[00727] Step B: tert-butyl 4-((5-amino-1-phenyl-1H-pyrazol-3-yl)methoxy)piperidine-1-carboxylate: A solution of diisopropylamine (1.08 mL, 7.74 mmol) in dry THF (5 mL) was cooled to 0 °C and 2.5M nBuLi in hexanes (2.96 mL, 7.41 mmol) was slowly added. The mixture was stirred at 0 °C for 10 minutes and was cooled to -78 °C. Acetonitrile (0.404 mL, 7.74 mmol) was added and the mixture was stirred for 15 minutes. A solution of tert-butyl 4-(2-ethoxy-2-oxoethoxy)piperidine-1-carboxylate (0.967 g, 3.37 mmol) in THF (2.5 mL) was added and the mixture was stirred at -78 °C for 1 hour. The mixture was allowed to reach ambient temperature, was quenched with ice water and concentrated. The residual aqueous mixture was neutralized with 2M HCl and was extracted with CH₂Cl₂ (3X). The combined organic fractions were dried over MgSO₄, filtered and concentrated to provide the crude cyano-ketone as a yellow oil that was used immediately in the next step.

[00728] Step C: tert-butyl 4-((5-amino-1-phenyl-1H-pyrazol-3-yl)methoxy)piperidine-1-carboxylate: The crude oil obtained in Step B was dissolved in EtOH (17 mL) and phenylhydrazine (0.396 mL, 3.99 mmol) was added. The mixture was heated at 60°C for 60 hours, was cooled to ambient temperature and was concentrated. The residue was partitioned into EtOAc and water, mixed and the organic layer removed. The aqueous layer was extracted

with EtOAc (2X) and the combined EtOAc portions were dried over MgSO_4 , filtered and concentrated. The residual orange oil was purified by silica chromatography using a 10-100% EtOAc/hexanes gradient elution. The pooled product fractions were concentrated and the residual yellow-orange oil was re-purified by reverse phase HPLC using a 0-100% acetonitrile/water gradient to provide the title compound as an orange foam (0.264 g, 21% yield). MS (apci) $m/z = 373.2$ (M+H).

Intermediate 189



1-phenyl-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-5-amine

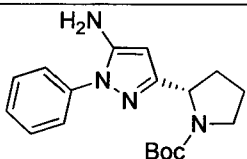
[00729] Step A: 3-oxo-3-(tetrahydro-2H-pyran-4-yl)propanenitrile: A 1M solution of LHMDS in dry THF (26.3 mL, 26.3 mmol) was cooled to -78°C and acetonitrile (1.43 mL, 27.5 mmol) was added dropwise over 2 minutes. The mixture was stirred at -78°C for 1 hour and a solution of methyl tetrahydro-2H-pyran-4-carboxylate (3.41 mL, 25.0 mmol) in dry THF (12 mL) was added. The mixture was stirred for 1 hour, the dry ice bath was removed and the mixture allowed to reach ambient temperature. The mixture was poured into chilled H_2O (250 mL) and was extracted with Et_2O (3X). The aqueous portion was cooled to 0°C and 6M HCl was added dropwise to pH=3 (starting pH=12). The mixture was extracted with EtOAc (3X) and the combined extracts were dried over MgSO_4 . The solution eluted through a SiO_2 plug eluting with EtOAc. The filtrate was concentrated to give the title compound as a colorless oil (2.52 g, 66%). ^1H NMR (CDCl_3) δ 3.99-4.06 (m, 2H), 3.54 (s, 2H), 3.46 (t, 2H), 2.76-2.86 (m, 1H), 1.70-1.86 (m, 4H).

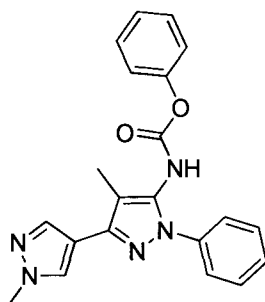
[00730] Step B: 1-phenyl-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-5-amine: To a solution of 3-oxo-3-(tetrahydro-2H-pyran-4-yl)propanenitrile (2.30 g, 12.8 mmol) in absolute EtOH (35 mL) was added phenylhydrazine hydrochloride (2.21 g, 15.3 mmol) and the mixture was heated at reflux until complete by TLC (5 hours). The mixture was cooled to ambient temperature and was concentrated. The residue was partitioned in H_2O (75 mL) and EtOAc (40 mL). 2M NaOH was added to pH=5 with vigorous mixing, the organic layer was removed and the aqueous was extracted with EtOAc (2X). The combined EtOAc fractions were washed with H_2O and saturated NaCl. The solution was diluted with an equal volume of hexanes, dried over MgSO_4 /activated carbon and eluted through a SiO_2 plug eluting with 50% EtOAc-hexanes. The filtrate was concentrated to give a gold syrup. The syrup was treated with Et_2O and stirred until a fine, granular suspension formed. The solid was collected, washed with Et_2O and dried in

vacuum to furnish the title compound as a white solid (2.01 g, 65%). ^1H NMR (CDCl_3) δ 7.55 (d, 2H), 7.46 (t, 2H), 7.32 (t, 1H), 5.49 (s, 1H), 4.00-4.08 (m, 2H), 3.97 (br s, 2H), 3.52 (dt, 2H), 2.86 (m, 1H) 1.73-1.93 (m, 4H).

[00731] The following compounds were prepared according to the method used for the preparation of 1-phenyl-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-5-amine (Intermediate 189) using either acetonitrile or propionitrile in Step A in conjunction with the appropriate ester.

Intermediate #	Structure	Data
190		MS (apci) m/z = 343.1 (M+H)
191		MS (apci) m/z = 258.0 (M+H)
192		^1H NMR (CDCl_3) δ 7.62 (d, 2H), 7.50 (t, 2H), 7.37 (t, 1H), 5.72 (s, 1H), 3.91 (br s, 2H), 2.58 (s, 3H), 2.44 (s, 3H).
193		^1H NMR (CDCl_3) δ 7.60 (d, 2H), 7.49 (t, 2H), 7.37 (t, 1H), 6.45 (s, 1H), 3.67 (br s, 2H), 2.45 (s, 3H), 2.24 (s, 3H).
194		^1H NMR (CDCl_3) δ 7.45-7.56 (m, 4H), 7.35 (t, 1H), 4.00-4.06 (m, 2H), 3.88 (dt, 2H), 3.62 (br s, 2H), 2.18-2.34 (m, 4H), 2.11 (s, 3H).
195		MS (apci) m/z = 343.2 (M+H)
196		MS (apci) m/z = 343.2 (M+H)
197		MS (apci) m/z = 329.2 (M+H)

Intermediate #	Structure	Data
198		MS (apci) m/z = 329.2 (M+H)

Intermediate 199Phenyl 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-ylcarbamate

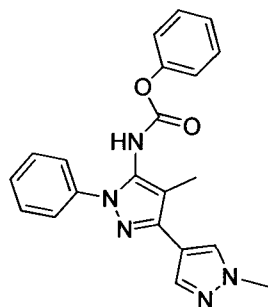
[00732] Step A: ethyl 1-methyl-1H-pyrazole-4-carboxylate: To a 3000-mL three-necked flask was added ethyl 2-formyl-3-oxopropanoate (100 g, 694 mmol), followed by anhydrous 200-proof EtOH (694 mL) to obtain a clear yellowish solution. The reaction was cooled in an ice bath to 5 °C, and then methylhydrazine (35.8 mL, 680 mmol) was added dropwise. A vigorous exotherm was observed during hydrazine addition and the temperature was kept below 12 °C by controlling the addition rate. After the hydrazine addition was complete, the ice bath was removed, and the reaction was allowed to stir at ambient temperature overnight. The reaction was concentrated on a rotary evaporator to a crude orange oil. The crude was taken up in DCM and re-concentrated, then on high vacuum for 2 days to yield tan orange oil. LC/MS and ¹H NMR showed essentially pure ethyl 1-methyl-1H-pyrazole-4-carboxylate (106 g, 99.1%).

[00733] Step B: 2-methyl-3-(1-methyl-1H-pyrazol-4-yl)-3-oxopropanenitrile: To a four-necked 5-liter round bottomed flask fitted with an overhead stirrer and addition funnel was charged LHMDs (1444 mL, 1444 mmol) (1.0M in THF). The solution was cooled in an acetone/dry ice bath first (internal temperature of -79 °C) under nitrogen, followed by slow addition of propionitrile (103 mL, 1444 mmol) via dropping funnel. The mixture was stirred at -80 °C for 90 minutes. A solution of ethyl 1-methyl-1H-pyrazole-4-carboxylate (106 g, 688 mmol) in anhydrous THF (500 mL) was then introduced dropwise via an addition funnel (addition time: about 45 minutes; internal temperature during addition remained below -76 °C). After the addition was complete, the reaction was allowed to slowly warm to ambient temperature and stirred overnight. An orange glass deposited on the bottom of the flask. The organics were decanted and the glass was dissolved in warm water. The mixture was washed

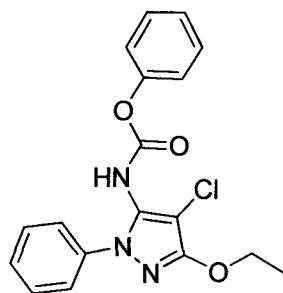
with with ether (3 x 1000 mL). The aqueous phase was then pH-adjusted to 5 (pH paper) using concentrated HCl and saturated bicarbonate solution. The aqueous layer was extracted with DCM (3 x 1000 mL). The combined organic extracts were dried over MgSO_4 filtered and concentrated to yield the 2-methyl-3-(1-methyl-1H-pyrazol-4-yl)-3-oxopropanenitrile as an amber oil (92 g, 82%). MS (apci) m/z = 162.1 (M-H).

[00734] Step C: 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-amine: A 3L, 3 necked round bottomed flask was charged with 2-methyl-3-(1-methyl-1H-pyrazol-4-yl)-3-oxopropanenitrile (60 g, 368 mmol) absolute anhydrous ethanol (1000 mL) and phenylhydrazine hydrochloride (58 g, 404 mmol) at ambient temperature to form a yellowish suspension. The reaction vessel was equipped with a water condenser and refluxed (using a heating mantle) overnight. The reaction was concentrated and 1M NaOH (1L) was added and the solid was broken up and collected. The solid was washed with water and hexanes. A second crop crashed out in the filtrate and was collected. The combined solids were crushed and triturated with ether (500 mL). The solid was collected filtration, washed with hexanes and air dried under vacuum to provide 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-amine (93 g, 100%).

[00735] Step D: phenyl 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-ylcarbamate: In a 3 L, round bottomed flask was charged with 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-amine (50 g, 197.4 mmol) and EtOAc (1000 mL) to obtain a clear brownish solution. To this was added NaOH (2M aq) (500 mL) in one portion to obtain a turbid mixture (both the aqueous and organic layers were clear but a precipitate was observed in between the two layers). After 3 minutes, phenyl carbonochloridate (74.29 mL, 592.2 mmol) was added slowly at ambient temperature exotherm to 33 °C. The reaction stirred at ambient temperature for 2 hours. Additional phenyl carbonochloridate (10 mL) was added. After 30 minutes the organics were separated, washed with brine and concentrated in vacuo. The product was purified by silica gel chromatography (eluting with 75% ethyl acetate in hexanes) to provide phenyl 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-ylcarbamate (60 g, 81.4%).

Intermediate 200phenyl 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-ylcarbamate

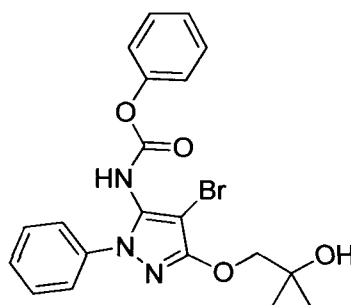
[00736] A 3 L, round bottomed flask was charged with 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-amine (50 g, 197.4 mmol) and EtOAc (1000 mL) to obtain a clear brownish solution. To this was added NaOH (2M aq) (500mL) in one portion to obtain a turbid mixture (the aqueous and organic layers were clear, but a precipitate was observed in between the two layers). After 3 minutes, phenyl carbonochloridate (74.29 mL, 592.2 mmol) was added slowly at ambient temperature (the temperature of the reaction mixture increased to 33 °C during the addition). The reaction stirred at ambient temperature for 2 hours. Additional phenyl carbonochloridate (10 mL) was added. After 30 minutes the organics layers were separated, washed with brine and concentrated in vacuo. The residue was purified by silica gel chromatography (eluting with 75% ethyl acetate in hexanes) to provide phenyl 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-ylcarbamate (60 g, 81.4%).

Intermediate 201phenyl (4-chloro-3-ethoxy-1-phenyl-1H-pyrazol-5-yl)carbamate

[00737] Step A: Preparation of phenyl (3-ethoxy-1-phenyl-1H-pyrazol-5-yl)carbamate: To a suspension of 3-ethoxy-1-phenyl-1H-pyrazol-5-amine (Intermediate P139, 169 mg, 0.832 mmol) in EtOAc (5 mL) at 0 °C was added 2.0 M aqueous NaOH solution (1.25 mL, 2.50 mmol), followed by dropwise addition of phenyl carbonochloridate (0.178 mL, 1.41 mmol). The reaction was stirred at ambient temperature for 15 hours. The reaction mixture was diluted with EtOAc and phase-separated. The organic layer was washed with water and brine, dried over MgSO₄, and concentrated. The residue was purified by flash chromatography on silica gel (6:1 hexanes:EtOAc) to give the title compound (219 mg, 81% yield). MS (apci) m/z = 324.1 (M+H).

[00738] Step B: Preparation of phenyl (4-chloro-3-ethoxy-1-phenyl-1H-pyrazol-5-yl)carbamate: To a solution of phenyl 3-ethoxy-1-phenyl-1H-pyrazol-5-ylcarbamate (92 mg, 0.28 mmol) and pyridinium 4-methylbenzenesulfonate (7.2 mg, 0.028 mmol) in DCM (2 mL) was added *N*-chlorosuccinimide (42 mg, 0.31 mmol) at ambient temperature. The mixture was stirred at ambient temperature for 2 days and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (9:1, hexanes/EtOAc) to give the title compound (76 mg, 75% yield). MS (apci) $m/z = 358.1$ (M+H).

Intermediate 203



Phenyl (4-bromo-3-(2-hydroxy-2-methylpropoxy)-1-phenyl-1H-pyrazol-5-yl)carbamate

[00739] Step A: Preparation of 5-amino-1-phenyl-1H-pyrazol-3(2H)-one: Prepared according to the method described for Intermediate P1, replacing 4,4-dimethyl-3-oxopentanenitrile with ethyl 2-cyanoacetate, and substituting phenylhydrazine for ethyl 3-hydrazinylbenzoate hydrochloride. MS (apci) $m/z = 176.0$ (M+H).

[00740] Step B: Preparation of 1-((5-amino-1-phenyl-1H-pyrazol-3-yl)oxy)-2-methylpropan-2-ol: A mixture of 5-amino-1-phenyl-1H-pyrazol-3(2H)-one (0.330 g, 1.88 mmol), 2,2-dimethyloxirane (0.143 g, 1.98 mmol) and K_2CO_3 (0.521 g, 3.77 mmol) in DMA (5 mL) was heated at 80 °C for 3 days. After cooling, the reaction mixture was diluted with EtOAc, washed with water and brine and dried over $MgSO_4$. The mixture was filtered through a pad of SiO_2 eluting with EtOAc to yield the title compound. MS (apci) $m/z = 248.1$ (M+H).

[00741] Step C: Preparation of phenyl (3-(2-hydroxy-2-methylpropoxy)-1-phenyl-1H-pyrazol-5-yl)carbamate: Prepared according to the method described for Intermediate 201. Step A using 1-((5-amino-1-phenyl-1H-pyrazol-3-yl)oxy)-2-methylpropan-2-ol as a replacement for 3-ethoxy-1-phenyl-1H-pyrazol-5-amine. MS (apci) $m/z = 368.1$ (M+H).

[00742] Step D: Preparation of phenyl (4-bromo-3-(2-hydroxy-2-methylpropoxy)-1-phenyl-1H-pyrazol-5-yl)carbamate: Prepared according to the method described for Intermediate 201, Step B using *N*-bromosuccinimide as a replacement for *N*-chlorosuccinimide, and substituting phenyl (3-(2-hydroxy-2-methylpropoxy)-1-phenyl-1H-pyrazol-5-yl)carbamate for phenyl 3-ethoxy-1-phenyl-1H-pyrazol-5-ylcarbamate. MS (apci) $m/z = 446.1$ (M+H).

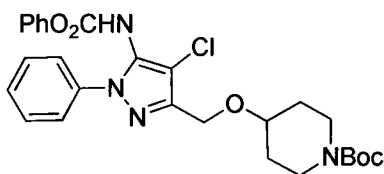
[00743] The following compounds prepared according to the method describe for the preparation of Intermediate 200, using the appropriate amino pyrazole intermediate:

Intermediate #	Structure	Name	Data
204		phenyl 3-(3-methoxypropyl)-4-methyl-1-phenyl-1H-pyrazol-5-ylcarbamate	MS (apci) m/z = 366.1 (M+H).
205		phenyl 3-(1,1-difluoro-2-hydroxyethyl)-4-methyl-1-phenyl-1H-pyrazol-5-ylcarbamate	MS (apci) m/z = 374.1 (M+H).
206		(S)-phenyl 3-(2-hydroxypropyl)-4-methyl-1-phenyl-1H-pyrazol-5-ylcarbamate	MS (apci) m/z = 352.1 (M+H).
207		(R)-phenyl 3-(2-hydroxypropyl)-4-methyl-1-phenyl-1H-pyrazol-5-ylcarbamate	MS (apci) m/z = 352.1 (M+H).
208		phenyl 3-(2-hydroxy-2-methylpropyl)-4-methyl-1-phenyl-1H-pyrazol-5-ylcarbamate	MS (apci) m/z = 366.2 (M+H).
209		phenyl 3-(3-hydroxycyclobutyl)-4-methyl-1-phenyl-1H-pyrazol-5-ylcarbamate	MS (apci) m/z = 364.2 (M+H).

Intermediate #	Structure	Name	Data
210		phenyl 3-(2-hydroxyethyl)-4-methyl-1-phenyl-1H-pyrazol-5-ylcarbamate	MS (apci) m/z = 338.1 (M+H).
211		ethyl 4-methyl-5-(phenoxycarbonylamino)-1-phenyl-1H-pyrazole-3-carboxylate	MS (apci) m/z = 366.1 (M+H).
212		phenyl 4-methyl-3-(methylcarbamoyl)-1-phenyl-1H-pyrazol-5-ylcarbamate	MS (apci) m/z = 351.1 (M+H).
213		phenyl 3-carbamoyl-4-methyl-1-phenyl-1H-pyrazol-5-ylcarbamate	MS (apci) m/z = 337.1 (M+H).
214		phenyl (4-methyl-3-(5-methyl-1,3,4-oxadiazol-2-yl)-1-phenyl-1H-pyrazol-5-yl)carbamate	MS (apci) m/z = 376.1 (M+H).
215		phenyl 4-methyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1-phenyl-1H-pyrazol-5-ylcarbamate	MS (apci) m/z = 376.1 (M+H).
216		phenyl 4-methyl-1-phenyl-3-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-5-ylcarbamate	MS (apci) m/z = 430.1 (M+H).

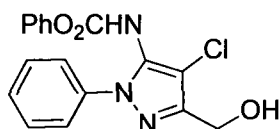
Intermediate #	Structure	Name	Data
217		tert-butyl 4-(5-((phenoxycarbonyl)amino)-1-phenyl-1H-pyrazol-3-yl)piperidine-1-carboxylate	MS (apci) m/z = 463.3 (M+H)
218		phenyl (4-methyl-1-phenyl-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-5-yl)carbamate	MS (apci) m/z = 378.2 (M+H)
219		phenyl (3-(3,5-dimethylisoxazol-4-yl)-1-phenyl-1H-pyrazol-5-yl)carbamate	¹ H NMR (CDCl ₃) δ 7.56-7.64 (m, 4H), 7.48-7.52 (m, 1H), 7.40 (t, 2H), 7.26 (t, 2H), 7.16 (br s, 2H), 6.71 (br s, 1H), 2.60 (s, 3H) 2.46 (s, 3H)
220		phenyl (4-methyl-3-(5-methylisoxazol-3-yl)-1-phenyl-1H-pyrazol-5-yl)carbamate	¹ H NMR (CDCl ₃) δ 7.54 (d, 2H), 7.49 (t, 2H), 7.41 (t, 1H), 7.33 (br s, 2H), 7.20 (br s, 1H), 7.08 (br s, 1H), 6.74 (br s, 1H), 6.66 (br s, 1H), 6.48 (s, 1H), 2.45 (s, 3H) 2.34 (s, 3H)
221		phenyl (3-(4-cyanotetrahydro-2H-pyran-4-yl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)carbamate	¹ H NMR (CDCl ₃) δ 7.06-7.56 (m, 9H), 6.75 (br s, 1H), 6.51 (s, 1H), 4.04 (d, 2H) 3.89 (t, 2H), 2.20-2.39 (m, 4H), 2.28 (s, 3H)

Intermediate #	Structure	Name	Data
222		(R)-tert-butyl 2-(4-methyl-5-((phenoxy carbonyl)amino)-1-phenyl-1H-pyrazol-3-yl)pyrrolidine-1-carboxylate	MS (apci) m/z = 463.2 (M+H)
223		(S)-tert-butyl 2-(4-methyl-5-((phenoxy carbonyl)amino)-1-phenyl-1H-pyrazol-3-yl)pyrrolidine-1-carboxylate	MS (apci) m/z = 463.2 (M+H)
224		(R)-tert-butyl 2-(5-((phenoxy carbonyl)amino)-1-phenyl-1H-pyrazol-3-yl)pyrrolidine-1-carboxylate	MS (apci) m/z = 449.2 (M+H)
225		(S)-tert-butyl 2-(5-((phenoxy carbonyl)amino)-1-phenyl-1H-pyrazol-3-yl)pyrrolidine-1-carboxylate	MS (apci) m/z = 449.2 (M+H)
226		tert-butyl 4-((5-((phenoxy carbonyl)amino)-1-phenyl-1H-pyrazol-3-yl)methoxy)piperidine-1-carboxylate	MS (apci) m/z = 493.2 (M+H)
227		phenyl (3-(hydroxymethyl)-1-phenyl-1H-pyrazol-5-yl)carbamate	MS (apci) m/z = 310.1 (M+H)

Intermediate 228

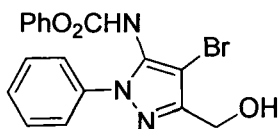
tert-butyl 4-((4-chloro-5-((phenoxycarbonyl)amino)-1-phenyl-1H-pyrazol-3-yl)methoxy)piperidine-1-carboxylate

[00744] To a suspension of tert-butyl 4-((5-(phenoxycarbonylamino)-1-phenyl-1H-pyrazol-3-yl)methoxy)piperidine-1-carboxylate (Intermediate 226), 98.5 mg, 0.200 mmol) in DCM (2.0 mL) was added pyridinium 4-methylbenzenesulfonate (PPTS) (5.03 mg, 0.020 mmol) and *N*-chlorosuccinimide (40.1 mg, 0.300 mmol). The resulting solution was stirred at ambient temperature for 8 days. The mixture was diluted with water and CH₂Cl₂, the organic layer was separated and the aqueous was extracted with CH₂Cl₂ (2X). The combined organic fractions were dried over MgSO₄, filtered and concentrated. The residue was purified by silica chromatography using 30-40% EtOAc/hexanes gradient elution to afford the title compound as an orange oil (73.5 mg, 70% yield). MS (apci) *m/z* = 527.2 (M+H).

Intermediate 229

Phenyl (4-chloro-3-(hydroxymethyl)-1-phenyl-1H-pyrazol-5-yl)carbamate

[00745] Prepared from phenyl 3-(hydroxymethyl)-1-phenyl-1H-pyrazol-5-ylcarbamate (Intermediate 227) using the procedure outlined for the preparation of tert-butyl 4-((4-chloro-5-((phenoxycarbonyl)amino)-1-phenyl-1H-pyrazol-3-yl)methoxy)piperidine-1-carboxylate (Intermediate 228). In this instance, the compound was isolated a white solid (108 mg, 28%). MS (apci) *m/z* = 344.0 (M+H).

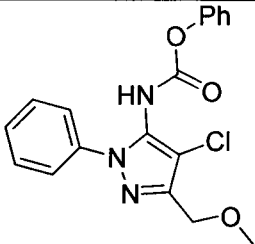
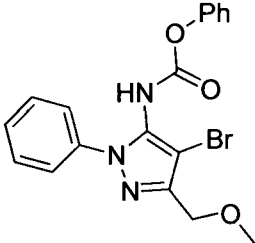
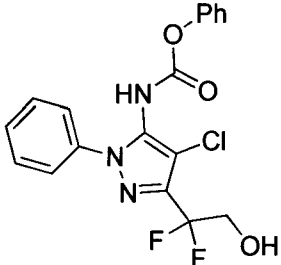
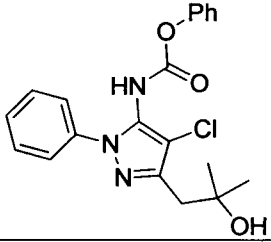
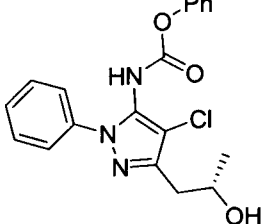
Intermediate 230

Phenyl (4-bromo-3-(hydroxymethyl)-1-phenyl-1H-pyrazol-5-yl)carbamate

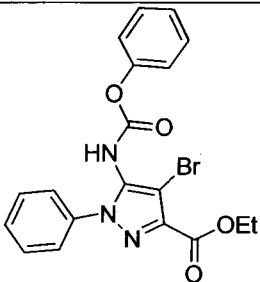
[00746] To a suspension of phenyl 3-(hydroxymethyl)-1-phenyl-1H-pyrazol-5-ylcarbamate (Intermediate 227, 100 mg, 0.323 mmol) in CH₂Cl₂ (1.6 mL) was added pyridinium 4-methylbenzenesulfonate (PPTS) (8.12 mg, 0.0323 mmol) and *N*-bromosuccinimide (86.3 mg, 0.485 mmol). The reaction mixture was stirred for 16 hours at ambient temperature. The

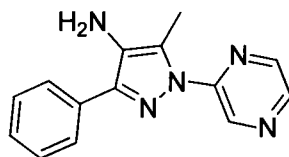
resulting suspension was filtered and the collected solid washed briefly with CH_2Cl_2 and dried in vacuum to afford the title compound a white solid (48.5 mg, 39%). MS (apci) $m/z = 388.0$ (M+H).

[00747] The following pyrazole intermediates were made according to the methods described for the preparation of Intermediate 228, 229 or 230.

Intermediate	Structure	Name	MS (apci) m/z
231		phenyl (4-chloro-3-(methoxymethyl)-1-phenyl-1H-pyrazol-5-yl)carbamate	358.1 (M+H)
232		phenyl (4-bromo-3-(methoxymethyl)-1-phenyl-1H-pyrazol-5-yl)carbamate	402.2 (M+H)
233		phenyl (4-chloro-3-(1,1-difluoro-2-hydroxyethyl)-1-phenyl-1H-pyrazol-5-yl)carbamate	394.1 (M+H)
234		phenyl (4-chloro-3-(2-hydroxy-2-methylpropyl)-1-phenyl-1H-pyrazol-5-yl)carbamate	386.1 (M+H)
235		(S)-phenyl (4-chloro-3-(2-hydroxypropyl)-1-phenyl-1H-pyrazol-5-yl)carbamate	372.1 (M+H)

Intermediate	Structure	Name	MS (apci) m/z
236		(R)-phenyl (4-chloro-3-(2-hydroxypropyl)-1-phenyl-1H-pyrazol-5-yl)carbamate	372.1 (M+H)
237		(R)-phenyl (4-bromo-3-(2-hydroxypropyl)-1-phenyl-1H-pyrazol-5-yl)carbamate	416.0 (M+H)
238		phenyl (4-chloro-3-(3-hydroxycyclobutyl)-1-phenyl-1H-pyrazol-5-yl)carbamate	384.1 (M+H)
239		phenyl 4-chloro-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1-phenyl-1H-pyrazol-5-ylcarbamate	396.0 (M+H)
240		phenyl (4-chloro-3-(2-hydroxy-2-methylpropoxy)-1-phenyl-1H-pyrazol-5-yl)carbamate	446.1 (M+H)
241		phenyl (4-chloro-3-(2-hydroxy-2-methylpropoxy)-1-phenyl-1H-pyrazol-5-yl)carbamate	388.1 (M+H)
242		phenyl (4-bromo-3-(2-hydroxy-2-methylpropoxy)-1-phenyl-1H-pyrazol-5-yl)carbamate	433.0 (M+H)

Intermediate	Structure	Name	MS (apci) m/z
243		ethyl 4-bromo-5-((phenoxycarbonyl)amino)-1-phenyl-1H-pyrazole-3-carboxylate	430.0 (M+H)

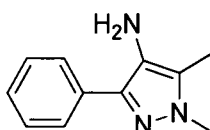
Intermediate 2455-methyl-3-phenyl-1-(pyrazin-2-yl)-1H-pyrazol-4-amine

[00748] Step A: 2-(5-methyl-4-nitroso-3-phenyl-1H-pyrazol-1-yl)pyrazine. To a solution of 2-hydrazinylpyrazine (0.485 g, 4.40 mmol) in HOAc (6 mL) was added (2-(hydroxyimino)-1-phenylbutane-1,3-dione (0.765 g, 4.00 mmol) in small portions over 2 minutes. The mixture was stirred for 5 minutes and the resulting light orange suspension was stirred at 60 °C for 6 hours. EtOH (1 mL) was added and the mixture was heated at 60 °C for an additional 6 hours. The resulting dark green suspension was cooled to ambient temperature and the mixture was diluted with H₂O (30 mL). The green suspension was stirred for 1 hour and the solid was collected via vacuum filtration. The collected solid was washed with H₂O and dried in vacuum. The solid was suspended in EtOH (25 mL) and concentrated HCl (500 µL) was added. The mixture was heated at reflux for 20 hours, cooled to ambient temperature and diluted with chilled H₂O (75 mL). The mixture was treated with 1M NaOH to pH=7 and was extracted with Et₂O (3X). The combined extracts were washed with saturated NaCl and dried over MgSO₄. The dried solution was filtered through packed Celite® and concentrated. The residual green-yellow solid was purified on a SiO₂ column using step gradient elution (25% CH₂Cl₂, 50% EtOAc/hexanes) to furnish the title compound as a turquoise solid (325 mg, 31%). MS (apci) m/z = 266.1 (M+H).

[00749] Step B: 5-methyl-3-phenyl-1-(pyrazin-2-yl)-1H-pyrazol-4-amine. To a mixture of 2-(5-methyl-4-nitroso-3-phenyl-1H-pyrazol-1-yl)pyrazine (325 mg, 1.04 mmol) and Zn dust (340 mg, 5.21 mmol) in EtOH (10 mL) was added concentrated HCl (95.5 µL, 1.15 mmol). The mixture was stirred at ambient temperature for 17 hours, then at 65 °C for 3 hours. The mixture was cooled to ambient temperature and was filtered through packed Celite® eluting with MeOH. The eluent was concentrated, and the residue was treated with H₂O and mixed. The resulting

orange suspension treated with 2M HCl to pH=1 and the mixture was extracted with Et₂O (3X). The aqueous portion was treated with 2M NaOH to pH=8 and extracted with EtOAc (3X). The combined EtOAc extracts were washed with saturated NaCl and dried over MgSO₄/activated carbon. The solution was eluted through a SiO₂ plug eluting with EtOAc. The eluent was concentrated to give the title compound as a light yellow wax (33 mg, 13%). MS (esi) m/z = 252.2 (M+H).

Intermediate 246

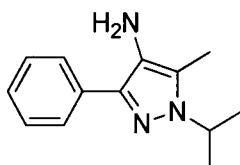


1,5-dimethyl-3-phenyl-1H-pyrazol-4-amine

[00750] Step A: 1,5-dimethyl-4-nitroso-3-phenyl-1H-pyrazole: To a solution of methylhydrazine (0.484 g, 10.5 mmol) in HOAc (10 mL) was added 2-(hydroxyimino)-1-phenylbutane-1,3-dione (2.01 g, 10.5 mmol) in small portions over 5 minutes. The reaction mixture was heated at 60 °C for 1 hour and was cooled to ambient temperature. Et₂O (50 mL) and H₂O (10 mL) were added to the mixture followed by slow addition of saturated Na₂CO₃ until pH=8 was obtained. The organic layer was removed and the aqueous layer was extracted with Et₂O (2X). The combined organic fractions were dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel chromatography (1:5 EtOAc/hexanes) to give the title compound as a green solid (1.32 g, 63%). MS (apci) m/z = 202.1 (M+H).

[00751] Step B: 1,5-dimethyl-3-phenyl-1H-pyrazol-4-amine: To a solution of 1,5-dimethyl-4-nitroso-3-phenyl-1H-pyrazole (1.32 g, 6.60 mmol) in MeOH (50 mL) was added Pd(OH)₂ on carbon (200 mg, 20 wt%, 0.286 mmol) and the reaction mixture was shaken under 50 psi of H₂ for 3 hours at ambient temperature. The reaction mixture was evacuated, purged with N₂ filtered through a pad of Celite® with MeOH elution. The eluent was concentrated and the residue dried in vacuum to provide the title compound as a tan solid (1.23 g, 100%). MS (apci) m/z = 188.1 (M+H).

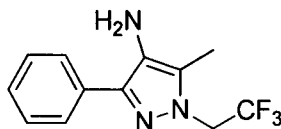
Intermediate 247



1-isopropyl-5-methyl-3-phenyl-1H-pyrazol-4-amine

[00752] The title compound was prepared according to the method described for Intermediate 246, using isopropylhydrazine hydrochloride in place of methylhydrazine in Step A to provide 620 mg (57%) of the title compound over 2 steps. MS (apci) $m/z = 216.1$ (M+H).

Intermediate 248

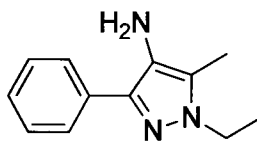


5-methyl-3-phenyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-amine

[00753] Step A: 5-methyl-4-nitroso-3-phenyl-1-(2,2,2-trifluoroethyl)-1H-pyrazole: The title compound was prepared using (2,2,2-trifluoroethyl)hydrazine in place of methylhydrazine in Step A of the procedure described for the preparation of 1,5-dimethyl-3-phenyl-1H-pyrazol-4-amine (Intermediate 246). The compound was isolated as a green solid (999 mg, 71%). ^1H NMR (CDCl_3) δ 7.60-7.73 (m, 5H), 4.70 (q, 2H), 2.27 (t, 3H).

[00754] Step B: 5-methyl-3-phenyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-amine: To a mixture of 5-methyl-4-nitroso-3-phenyl-1-(2,2,2-trifluoroethyl)-1H-pyrazole (50 mg, 0.186 mmol) and Zn dust (60.7 mg, 0.929 mmol) in EtOH (0.4 mL) was added concentrated HCl (17.0 μL , 0.204 mmol) and the mixture was heated at reflux for 3 hours. The mixture was cooled to ambient temperature and was diluted with MeOH and filtered. The filtrate was concentrated and the residue was diluted in water. The aqueous mixture was treated with saturated NaHCO_3 until pH=10 was achieved. The mixture was extracted with DCM (3X) and the combined extracts were dried over Na_2SO_4 , filtered and concentrated afford the title compound as a yellow oil (47.1 mg, 99.4% yield). MS (apci) $m/z = 256.1$ (M+H).

Intermediate 249

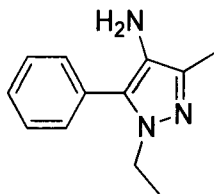


1-ethyl-5-methyl-3-phenyl-1H-pyrazol-4-amine

[00755] Step A: 1-ethyl-5-methyl-4-nitroso-3-phenyl-1H-pyrazole: The title compound was prepared according to the procedure described for the preparation of Intermediate 246, using ethylhydrazine oxalate in place of methylhydrazine in Step A. 1-Ethyl-5-methyl-4-nitroso-3-phenyl-1H-pyrazole was isolated as a green oil (288 mg, 26%). ^1H NMR (CDCl_3) δ 8.19 (d, 2H), 7.46-7.50 (m, 3H), 4.15 (q, 2H), 2.43 (s, 3H), 1.50 (t, 3H). The minor regioisomer, 1-ethyl-3-methyl-4-nitroso-5-phenyl-1H-pyrazole, was also obtained as a blue-green solid (165 mg, 15%). ^1H NMR (CDCl_3) δ 7.71 (dd, 2H), 7.59 (m, 3H), 4.17 (q, 2H), 2.28 (s, 3H), 1.51 (t, 3H).

[00756] Step B: 1-ethyl-5-methyl-3-phenyl-1H-pyrazol-4-amine: Prepared according to the procedure described for the preparation of Intermediate 248, using 1-ethyl-5-methyl-4-nitroso-3-phenyl-1H-pyrazole in Step B. the title compound was isolated as a light purple solid (281 mg, 104%). MS (apci) $m/z = 202.1$ (M+H).

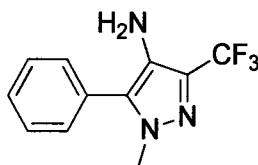
Intermediate 250



1-ethyl-3-methyl-5-phenyl-1H-pyrazol-4-amine

[00757] Prepared according to the procedure described for the preparation of Intermediate 249, using 1-ethyl-3-methyl-4-nitroso-5-phenyl-1H-pyrazole in Step A. The title compound was prepared according to Step B. The compound was isolated as a colorless oil (82.4 mg, 52.5%) after purification by reverse-phase chromatography. MS (apci) $m/z = 202.1$ (M+H).

Intermediate 251



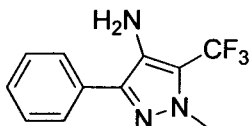
1-methyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-amine

[00758] Step A: 4,4,4-trifluoro-2-(hydroxyimino)-1-phenylbutane-1,3-dione: A solution of 4,4,4-trifluoro-1-phenylbutane-1,3-dione (5.00 g, 23.1 mmol) in HOAc (46.3 mL) was chilled to 10 °C and sodium nitrite (1.84 g, 26.6 mmol) in water (6.0 mL) was added. The mixture was stirred at ambient temperature for 90 minutes and was diluted with H₂O (150 mL). The mixture was extracted with Et₂O (3X) and the combined organic fractions were carefully washed with saturated NaHCO₃ until pH=9. The Et₂O solution was washed with H₂O and saturated NaCl and was dried over MgSO₄. The dried solution was filtered and concentrated to afford the title compound as a yellow foam (4.21 g, 74.2% yield). MS (apci) $m/z = 244.1$ (M-H).

[00759] Step B: 4-nitroso-3-phenyl-5-(trifluoromethyl)-1H-pyrazole: A solution of hydrazine monohydrate (0.204 g, 4.08 mmol) in EtOH (5 mL) was cooled to 0 °C and 4,4,4-trifluoro-2-(hydroxyimino)-1-phenylbutane-1,3-dione (1.00 g, 4.08 mmol) in EtOH (15 mL) was added. The reaction mixture was stirred at ambient temperature for 3 hours, excess powdered MgSO₄ was added and the mixture was heated at 60 °C for 16 hours. The mixture was cooled to ambient temperature, filtered and concentrated to afford the crude title compound as a green solid (78.7 mg, 8.0%) that was taken directly to the next step. MS (apci) $m/z = 240.0$ (M-H).

[00760] Step C: 1-methyl-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-amine: To a solution of 4-nitroso-3-phenyl-5-(trifluoromethyl)-1H-pyrazole (78.7 mg, 0.326 mmol) in DMF (1.6 mL) was added NaH (14.4 mg, 0.359 mmol) and the mixture was stirred at ambient temperature for 30 minutes. The mixture was treated with methyl iodide (40.6 μ L, 0.653 mmol) and stirred for 17 hours. The reaction mixture was directly purified by reverse phase HPLC using 20-100% acetonitrile/water gradient elution to provide a light blue solid (40.2 mg). The solid was dissolved in EtOH (0.35 mL) and was subjected to the reduction procedure described in Step B of the preparation of 5-methyl-3-phenyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-amine (Intermediate 248). The title compound was obtained as white solid (25.1 mg, 66.1%).

Intermediate 252

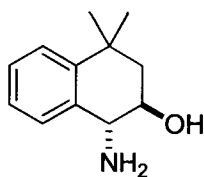


1-methyl-3-phenyl-5-(trifluoromethyl)-1H-pyrazol-4-amine

[00761] Step A: 1-methyl-4-nitroso-3-phenyl-5-(trifluoromethyl)-1H-pyrazole. To a solution of methylhydrazine (0.214 mL, 4.08 mmol) in EtOH (20 mL) was added 4,4,4-trifluoro-2-(hydroxyimino)-1-phenylbutane-1,3-dione (Intermediate 251, Step A; 1.00 g, 4.079 mmol). The reaction mixture was stirred at ambient temperature for 1 hour and excess MgSO_4 was added. The mixture was stirred at 60 $^{\circ}\text{C}$ for 48 hours and was cooled to ambient temperature. The mixture was filtered and the filtrate concentrated to a green residue. The residue was purified by silica gel chromatography using a 10-30% EtOAc/hexanes gradient for elution to provide the title compound as a green solid (482 mg, 46%). ^1H NMR (CDCl_3) δ 7.89 (d, 2H), 7.45-7.52 (m, 3H), 4.15 (s, 3H).

[00762] Step B: 1-methyl-3-phenyl-5-(trifluoromethyl)-1H-pyrazol-4-amine. Prepared from 1-methyl-4-nitroso-3-phenyl-5-(trifluoromethyl)-1H-pyrazole according to the method described for the preparation of Intermediate 248, Step B. The title compound was obtained as white solid (309 mg, 68%). ^1H NMR (CDCl_3) δ 7.65 (d, 2H), 7.45 (t, 2H), 7.35 (t, 1H), 3.93 (s, 3H), 3.52 (br s, 2H).

Intermediate X1



trans-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol

[00763] Step A: Preparation of 4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol: To a

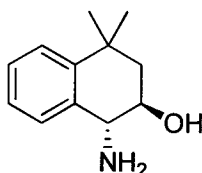
suspension of sodium borohydride (3.12 g, 82.5 mmol) in 4:1 THF:MeOH (250 mL) was added 4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (13.1 g, 75.0 mmol) dropwise over 15 minutes. The mixture was stirred at ambient temperature for 15 minutes and was quenched with 1M NaOH (50 mL). After stirring for 15 minutes, the mixture was concentrated and the aqueous residue was diluted with 1M NaOH (50 mL) and H₂O (50 mL). The mixture was extracted with hexanes (3X) and the combined extracts washed with H₂O and saturated NaCl. The organic portion was dried over MgSO₄/activated charcoal, filtered through packed Celite® and concentrated to provide the crude product as a faint yellow syrup after drying in vacuum (11.8 g, 89%). ¹H NMR (CDCl₃) δ 7.41 (dd, J=7.6, 1.6 Hz, 1H), 7.33 (dd, J=7.9, 1.5 Hz, 1H), 7.25 (dt, J=7.3, 1.6 Hz, 1H), 7.18 (dd, J=7.5, 1.5 Hz, 1H), 4.72 (dd, J=5.5, 5.1 Hz, 1H), 2.11-2.03 (m, 1H), 1.93-1.83 (m, 2H), 1.73 (br s, 1H), 1.63-1.57 (m, 1H), 1.33 (s, 3H), 1.24 (s, 3H) ppm.

[00764] Step B: Preparation of 1,1-dimethyl-1,2-dihydronaphthalene: To a solution of crude 4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (11.3 g, 64.1 mmol) in dry benzene (150 mL) was added MP-TsOH (0.788 g, 3.21 mmol, 4.07 mmol/g) and the mixture was stirred for 18 hours. Molecular sieves (4 angstrom, 10 g) and a second charge of MP-TsOH (0.80 g) were added and the mixture was stirred 6 hours. The mixture was filtered through a SiO₂ plug capped with a MgSO₄ layer (benzene elution) and concentrated. The residue was purified on a SiO₂ column (hexanes elution) to give the product as a colorless oil (4.54 g, 45%). ¹H NMR (CDCl₃) δ 7.29 (d, J=7.1 Hz, 1H), 7.20-7.12 (m, 2H), 7.04 (dd, J=7.2, 1.6 Hz, 1H), 6.45 (d, J=9.6 Hz, 1H), 5.93 (app. dt, J=9.6, 4.4 Hz, 2H), 2.24 (dd, J=4.4, 1.8 Hz, 2H), 1.24 (s, 6H) ppm.

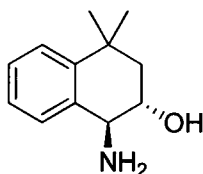
[00765] Step C: Preparation of 3,3-dimethyl-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene: To a solution of 1,1-dimethyl-1,2-dihydronaphthalene (2.64 g, 14.5 mmol) in toluene (60 mL) was added mCPBA (4.29 g, 17.4 mmol) and the reaction mixture was stirred at ambient temperature for 4.5 hours. The mixture was eluted through a SiO₂ plug capped with a layer of MgSO₄ (toluene for elution) and concentrated to provide the title compound as a colorless oil after drying in vacuum (1.62 g, 64%). ¹H NMR (CDCl₃) δ 7.44-7.13 (m, 4H), 3.84 (d, J=4.2, 1H), 3.72 (ddd, J=4.2, 2.1, 2.1, 1H), 2.21 (dd, J=15, 2.6 Hz, 1H), 1.83 (d, J=15 Hz, 1H), 1.35 (s, 3H), 1.31 (s, 3H) ppm.

[00766] Step D: Preparation of *trans*-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol: A sealed pressure vessel was charged with 3,3-dimethyl-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene (1.60 g, 8.26 mmol), 7M NH₃ in MeOH (30 mL) and concentrated NH₄OH (30 mL). The reaction vessel was sealed and the reaction mixture heated at 70 °C for 16 hours. The reaction was cooled to ambient temperature and concentrated to an aqueous mixture. The mixture was diluted with H₂O (50 mL) and extracted with EtOAc (3X). The extracts were

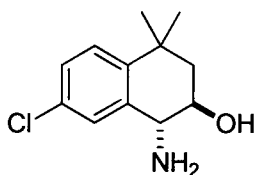
combined and washed with H₂O (2X) and saturated NaCl. The solution was dried over MgSO₄/activated charcoal, filtered and concentrated. The residual solid was washed with hexanes and dried in vacuum to provide the title compound as a white solid (1.17 g, 74%). ¹H NMR (CDCl₃) δ 7.46 (dd, 6.4, 4.7 Hz, 1H), 7.28 (m, 1H), 7.22 (m, 2H), 3.63 (m, 2H), 2.20 (br s, 3H), 1.99 (dd, J=13, 2.8 Hz, 1H), 1.75 (dd, J=12, 12 Hz, 1H), 1.35 (s, 3H), 1.31 (s, 3H) ppm.

Intermediate X2(1R,2R)-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol

[00767] The title compound was isolated as a white solid from separation of racemic *trans*-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Intermediate X1) using preparative chiral HPLC (Chiral Tech OD-H®, 5% EtOH/hexane, Peak 1).

Intermediate X3(1S,2S)-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol

[00768] The title compound was isolated as a white solid from separation of racemic *trans*-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Intermediate X1) using preparative chiral HPLC (Chiral Tech OD-H®, 5% EtOH/hexane, Peak 2).

Intermediate X4*trans*-1-amino-7-chloro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol

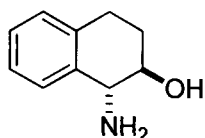
[00769] Step A: Preparation of 7-bromo-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol: 7-bromo-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (1.60 g, 6.32 mmol) was dissolved in MeOH (100 mL) and NaBH₄ (0.287 g, 7.58 mmol) was added in small portions. The reaction was stirred at ambient temperature for 1 hour and partially concentrated *in vacuo*. 2N NaOH (50 mL) was added and the mixture was extracted with EtOAc (2x 100 mL), filtered through phase separator paper and concentrated to afford 7-bromo-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (1.60 g, 6.27 mmol, 99.2 % yield). MS (apci) m/z = 255.1; 257.1 (M+H).

[00770] Step B: Preparation of 6-bromo-1,1-dimethyl-1,2-dihydronaphthalene: 7-bromo-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (1.60 g, 6.27 mmol) and MP-TsOH (1.17 g, 6.27 mmol) were combined in 50 mL of toluene and left to stand overnight. The reaction was filtered, concentrated and purified by silica gel column using 100% hexanes as the eluent to afford 6-bromo-1,1-dimethyl-1,2-dihydronaphthalene (520 mg, 2.19 mmol, 35.0 % yield). ¹H NMR (CDCl₃) δ 7.25-7.30 (m, 1H), 7.12-7.17 (m, 2H), 6.35-6.39 (m, 1H), 5.95-6.01 (m, 1H), 2.22-2.25 (m, 2H), 1.24 (s, 6H) ppm.

[00771] Step C: Preparation of 6-chloro-1,1-dimethyl-1,2-dihydronaphthalene: 6-bromo-1,1-dimethyl-1,2-dihydronaphthalene (200 mg, 0.843 mmol) was dissolved in THF (10 mL) and cooled to -78 °C. A solution of *tert*-BuLi in pentane (1637 μL, 2.78 mmol) was added dropwise and the reaction was stirred at -78 °C for 20 minutes. 1,1,1,2,2,2-hexachloroethane (477 μL, 4.22 mmol) was added and the reaction was allowed to warm to ambient temperature overnight, quenched with brine (10 ml) and extracted with EtOAc (2x25 mL). The combined organic extracts were filtered through phase separator paper and concentrated. The crude product was purified by silica gel column (100% hexanes) to afford 6-chloro-1,1-dimethyl-1,2-dihydronaphthalene (17 mg, 0.09 mmol, 10.5 % yield). ¹H NMR (CDCl₃) δ 7.18-7.22 (m, 1H), 7.11-7.14 (m, 1H), 6.99-7.01 (m, 1H), 6.35-6.40 (m, 1H), 5.95-6.01 (m, 1H), 2.22-2.26 (m, 2H), 1.24 (s, 6H) ppm.

[00772] Step D: Preparation of *trans*-1-amino-7-chloro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol: 6-chloro-1,1-dimethyl-1,2-dihydronaphthalene (15 mg, 0.08 mmol) was dissolved in DCM (5 mL) and NaHCO₃ (saturated aqueous, 5 ml) and stirred at 0 °C. mCPBA (20 mg, 0.08 mmol) was added and the reaction was allowed to warm to ambient temperature and stirred for 3 days. The mixture was extracted with several portions of DCM in a phase separator frit, concentrated, and taken up in concentrated ammonium hydroxide (906 μL, 8.1 mmol). The reaction was stirred at ambient temperature overnight and then in a 100 °C sand bath for 3h. The reaction was cooled and concentrated to afford *trans*-1-amino-7-chloro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (21 mg). This material contained some mCPBA-derived impurities but was used in subsequent reactions without purification. MS (apci) m/z = 226.1 (M+H).

Intermediate X5

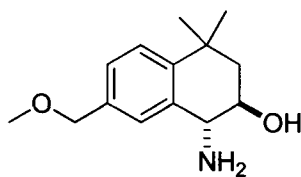


trans-1-amino-1,2,3,4-tetrahydronaphthalen-2-ol

[00773] Step A: Preparation of 1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene: 1,2-dihydronaphthalene (2.00 g, 15.4 mmol) was dissolved in DCM (75 mL) and saturated aqueous NaHCO_3 (75 mL) and cooled to 0 °C. mCPBA (4.17 g, 16.9 mmol) was added and the reaction was allowed to warm to ambient temperature overnight. The layers were separated and the aqueous layer was extracted with EtOAc (100 mL). The combined organic extracts were filtered through phase separator paper and concentrated to afford 1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene (2.20 g, 15.0 mmol, 98.0 % yield). MS (apci) m/z = 147.1 (M+H).

[00774] Step B: Preparation of *trans*-1-amino-1,2,3,4-tetrahydronaphthalen-2-ol: 1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene (1.00 g, 6.8 mmol) and NH_4OH (4.8 g, 136 mmol) were combined in a sealed tube and heated at 60 °C for 3 hours. The precipitate that formed was collected and washed with water and ether to afford *trans*-1-amino-1,2,3,4-tetrahydronaphthalen-2-ol (122 mg, 0.7475 mmol, 10.93 % yield). MS (apci) m/z = 147.1 (M- NH_3).

Intermediate X6



trans-1-amino-7-(methoxymethyl)-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol

[00775] Step A: Preparation of 7-(methoxymethyl)-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one: Potassium methoxymethyltrifluoroborate (1.20 g, 7.90 mmol), 7-bromo-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (1.00 g, 3.95 mmol), Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (0.645 g, 0.790 mmol) and Cs_2CO_3 (6.44 g, 19.8 mmol) were combined in dioxane (2 mL) and water (0.5 mL) and degassed by bubbling N_2 through the solution for 10 minutes. The reaction was then sealed in a glass tube and heated in a 100 °C sand bath for 6 hours and then in a 120 °C sand bath for 15 hours. The reaction was cooled, poured into brine (50 mL) and extracted with EtOAc (2x100 mL). The combined organic extracts were concentrated and purified by silica gel column (0-10% EtOAc/hexanes) to afford 7-(methoxymethyl)-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (162 mg, 0.742 mmol, 18.8 % yield). MS (apci) m/z = 219.1 (M+H).

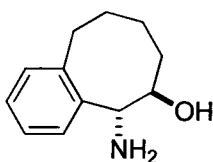
[00776] Step B: Preparation of 7-(methoxymethyl)-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol: 7-(methoxymethyl)-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (210 mg, 0.962 mmol) was dissolved in MeOH (20 mL) and NaBH_4 (54.6 mg, 1.44 mmol) was added in small portions. The reaction was stirred at ambient temperature for 1 hour and partially concentrated. 2N NaOH (20 mL) was added and the mixture was extracted with EtOAc (2x 50

mL), filtered through phase separator paper and concentrated to afford 7-(methoxymethyl)-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (203 mg, 0.921 mmol, 95.8 % yield). ^1H NMR (CDCl_3) δ 7.38-7.40 (m, 1H), 7.30-7.34 (m, 1H), 7.20-7.25 (m, 1H), 4.71-4.75 (m, 1H), 4.42 (s, 2H), 3.39 (s, 3H), 2.02-2.12 (m, 1H), 1.82-1.93 (m, 2H), 1.56-1.64 (m, 1H), 1.32 (s, 3H), 1.24 (s, 3H) ppm.

[00777] Step C: Preparation of 6-(methoxymethyl)-1,1-dimethyl-1,2-dihydronaphthalene: 7-(methoxymethyl)-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (130 mg, 0.590 mmol) was dissolved in 10 ml of dry ether and Martin Sulfurane (516 mg, 0.767 mmol) added. The reaction was stirred at ambient temperature overnight, 5 mL of 2M saturated aqueous Na_2CO_3 added and the reaction was stirred for 1 hour and filtered through Celite®. Brine was added to the filtrate and the mixture was extracted with several portions of EtOAc. The combined organic extracts were filtered through phase separator paper, concentrated and purified by silica gel column (0-10% EtOAc/hexanes) to afford 6-(methoxymethyl)-1,1-dimethyl-1,2-dihydronaphthalene (100 mg, 0.49 mmol, 83.8 % yield). MS (apci) $m/z = 203.1$ (M+H).

[00778] Step D: Preparation of *trans*-1-amino-7-(methoxymethyl)-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol: 6-(methoxymethyl)-1,1-dimethyl-1,2-dihydronaphthalene (100 mg, 0.494 mmol) was dissolved in DCM (10 mL) and saturated aqueous NaHCO_3 (10 ml) and stirred at 0 °C. mCPBA (183 mg, 0.742 mmol) was added and the reaction was allowed to warm to ambient temperature overnight. The mixture was extracted with several portions of DCM in a phase separator frit, concentrated, and taken up in concentrated ammonium hydroxide (2623.2 μL , 45.810 mmol). The reaction was stirred in a 60 °C sand bath for 2 hours, cooled and concentrated to afford *trans*-1-amino-7-(methoxymethyl)-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (100 mg, 0.42 mmol, 88 % yield for two steps). This material contained some impurities but was used in subsequent reactions without purification. MS (apci) $m/z = 219.1$ (M- NH_3).

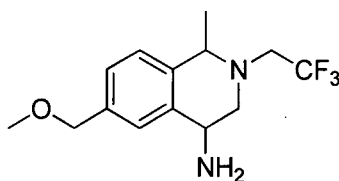
Intermediate X7



trans-5-amino-6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-ol

[00779] *trans*-5-amino-6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-ol was synthesized from 1-Benzosuberone in 23.9% overall yield using the method as described for Intermediate X1, Steps A-D. The obtained *trans*-5-amino-6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-ol contained some impurities but was used in subsequent reactions without purification MS (apci) $m/z =$

178.1 (M+H).

Intermediate X8

6-(methoxymethyl)-1-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-amine

[00780] Step A: Preparation of 2,2-dimethoxy-N-(1-(4-(methoxymethyl)phenyl)ethyl)ethanamine: 1-(4-(methoxymethyl)phenyl)ethanone (500 mg, 3.05 mmol) and 2,2-dimethoxyethanamine (480 mg, 4.57 mmol) were combined in 3 mL of CHCl_3 and stirred for 15 minutes. $\text{Na}(\text{OAc})_3\text{BH}$ (839 mg, 3.96 mmol) was added and the reaction was stirred for 2 hours. AcOH (1 drop) was added and the reaction was stirred at ambient temperature overnight, quenched with water (3 mL) and extracted with DCM (3x 10 mL) in a Phase Separator frit. The combined organic extracts were concentrated to afford 2,2-dimethoxy-N-(1-(4-(methoxymethyl)phenyl)ethyl)ethanamine (610 mg, 2.41 mmol, 79.1 % yield). MS (apci) m/z = 254.2 (M+H).

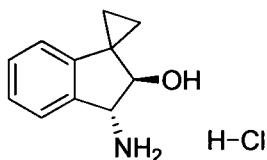
[00781] Step B: Preparation of N-(2,2-dimethoxyethyl)-2,2,2-trifluoro-N-(1-(4-(methoxymethyl)phenyl)ethyl)ethanamine: 2,2-dimethoxy-N-(1-(4-(methoxymethyl)phenyl)ethyl)ethanamine (250 mg, 0.987 mmol), NEt_3 (413 μL , 2.96 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (275 mg, 1.18 mmol) were combined and stirred at ambient temperature overnight, at 60 °C for 24 hours and then at 100 °C for 24 hours. The reaction was loaded onto a samplet and purified by reverse phase column (0-80% Acetonitrile/ H_2O) to afford N-(2,2-dimethoxyethyl)-2,2,2-trifluoro-N-(1-(4-(methoxymethyl)phenyl)ethyl)ethanamine (278 mg, 0.829 mmol, 84.0 % yield). MS (apci) m/z = 254.2 (M-MeOH).

[00782] Step C: Preparation of 6-(methoxymethyl)-1-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-ol: N-(2,2-dimethoxyethyl)-2,2,2-trifluoro-N-(1-(4-(methoxymethyl)phenyl)ethyl)ethanamine (330 mg, 0.984 mmol) and perchloric acid (70% in water, 2 mL) were combined and stirred at ambient temperature for 4 hours. The reaction was poured into a mixture of ice and 2N NaOH (50 mL) and extracted with several portions of EtOAc , filtered through PS paper and concentrated. The mixture was purified by reverse phase column using 0-70% acetonitrile/ H_2O as the eluent to afford 6-(methoxymethyl)-1-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-ol (143 mg, 0.494 mmol, 50.2 % yield) as a ~ 1:2 mixture of diastereomers. MS (apci) m/z = 290.1 (M+H)

[00783] Step D: Preparation of 4-azido-6-(methoxymethyl)-1-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinoline: 6-(methoxymethyl)-1-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-ol (25 mg, 0.086 mmol) was dissolved in DCM (2 mL) and thionyl chloride (13 μ L, 0.17 mmol) was added. The reaction was stirred at ambient temperature for 2h and then at 50 °C for 20 minutes, concentrated, and DMF and NaN₃ (52.8 mg, 0.812 mmol) were added. The reaction was stirred ambient temperature for 1 hour and then at 100 °C for 30 minutes. The mixture was loaded onto a samplet and purified by reverse phase column chromatography using 0-70% acetonitrile/H₂O as the eluent to afford 4-azido-6-(methoxymethyl)-1-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinoline (20 mg, 0.0636 mmol, 78.3 % yield). MS (apci) m/z = 287.1 (M-N₂).

[00784] Step E: Preparation of 6-(methoxymethyl)-1-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-amine: 4-azido-6-(methoxymethyl)-1-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinoline (20 mg, 0.064 mmol) and 10 % Pd/C (6.8 mg, 0.0064 mmol) were mixed in 1 mL of MeOH and stirred under a balloon of H₂ for 3 hours. The reaction was filtered and concentrated to afford 6-(methoxymethyl)-1-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-amine (18 mg, 0.062 mmol, 98 % yield) which was used without purification. MS (apci) m/z = 272.1 (M-NH₃).

Intermediate X9



(2'R,3'R)-3'-amino-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-ol hydrochloride

[00785] Step A: Preparation of *tert*-butyl (*trans*-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)carbamate: To a solution of *trans*-3'-amino-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-ol (Example 55, Step C, 425 mg, 2.425 mmol) in DCM (15 mL) were added DIEA (845 μ L, 4.851 mmol) and Boc₂O (582 mg, 2.668 mmol). The reaction mixture was stirred at ambient temperature for 22 hours, then diluted with H₂O (25 mL), extracted with DCM (2 x 25 mL), and the combined organic phases were washed with brine (40 mL), dried (MgSO₄), filtered, and concentrated to afford the product as a beige solid (636 mg, 95% yield).

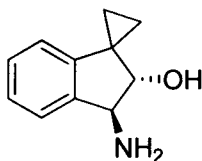
[00786] Step B: Preparation of *trans*-3'-((*tert*-butoxycarbonyl)amino)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-yl acetate: To a solution of *tert*-butyl (*trans*-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)carbamate (455 mg, 1.65 mmol) in pyridine (4.13 mL, 1.65 mmol) were added DMAP (20.2 mg, 0.165 mmol) then Ac₂O (468 μ L,

4.96 mmol). The reaction mixture was stirred at ambient temperature for 17 hours, then was diluted with aqueous HCl (1 M, 60 mL), then extracted with DCM (2 x 50 mL). The combined organic phases were washed with H₂O (50 mL), dried (MgSO₄), filtered, concentrated, and dried under high vacuum to afford the product as a brown solid (477 mg, 91% yield).

[00787] Step C: Preparation of (2'R,3'R)-3'-((tert-butoxycarbonyl)amino)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-yl acetate: Racemic *trans*-3'-((tert-butoxycarbonyl)amino)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-yl acetate (477 mg, 1.503 mmol) was separated by chiral HPLC (Chiral Tech OJ-H, 22 mm x 250 mm, 5 μ particle size, 7.5% ethanol : 92.5% hexanes, 22 mL/min, 220 nm). The first peak to elute was collected and concentrated to afford the product as a white solid (168 mg, 35% yield). ¹H NMR (CDCl₃) δ 7.33 (d, 1H), 7.28-7.19 (m, 2H), 6.71 (d, 1H), 5.28 (d, 1H), 5.20 (br m, 1H), 4.82 (br m, 1H), 2.07 (s, 3H), 1.48 (s, 9H), 1.25 (m, 1H), 1.16 (m, 1H), 1.00 (m, 1H), 0.88 (m, 1H).

[00788] Step D: Preparation of tert-butyl ((2'R,3'R)-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)carbamate: To a solution of (2'R,3'R)-3'-((tert-butoxycarbonyl)amino)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-yl acetate (168 mg, 0.529 mmol) in MeOH (2 mL) was added K₂CO₃ (109.7 mg, 0.794 mmol). The reaction mixture was stirred at ambient temperature for 2 hours, then diluted with 20% iPrOH / 80% DCM (10 mL), filtered through a plug of silica, rinsing with 20% iPrOH / 80% DCM (2 x 20 mL). The eluent was concentrated to afford the product as an off-white solid (145 mg, 99% yield). ¹H NMR (CDCl₃) δ 7.15-7.25 (m, 3H), 6.73 (d, 1H), 5.03 (br s, 1H), 4.93 (t, 1H), 4.25 (d, 1H), 1.52 (m, 1H), 1.48 (s, 9H), 1.10 (m, 1H), 0.96 (m, 1H), 0.60 (m, 1H).

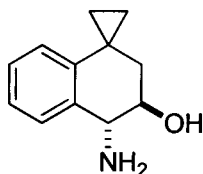
[00789] Step E: Preparation of (2'R,3'R)-3'-amino-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-ol hydrochloride: To a solution of tert-butyl ((2'R,3'R)-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)carbamate (145 mg, 0.527 mmol) in iPrOH (2.5 mL) was added HCl (5-6M in iPrOH, 1.05 mL). The reaction mixture was stirred at ambient temperature for 17 hours and then concentrated. The solid was diluted with Et₂O (1 mL) and concentrated (3x), then dried under high vacuum to afford the HCl salt of the product as a pale yellow solid (110 mg, 99% yield). ¹H NMR (CD₃OD) δ 7.43 (dd, 1H), 7.34 (tt, 1H), 7.26 (dt, 1H), 6.87 (br d, 1H), 4.51 (d, 1H), 4.25 (d, 1H), 1.41 (m, 1H), 1.16 (m, 1H), 1.02 (m, 1H), 0.75 (m, 1H).

Intermediate X10(2'S,3'S)-3'-amino-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-ol

[00790] Step A: Preparation of (2'S,3'S)-3'-((tert-butoxycarbonyl)amino)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-yl acetate: Racemic *trans*-3'-((tert-butoxycarbonyl)amino)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-yl acetate (Intermediate X9, Step B, 176 mg, 0.555 mmol) was separated by chiral HPLC (Chiral Tech OJ-H, 22 mm x 250 mm, 5 μ particle size, 7.5% ethanol : 92.5% hexanes, 22 mL/min, 220 nm). The second peak to elute was collected and concentrated to afford the product as a beige solid (63.4 mg, 36% yield). ^1H NMR (CDCl_3) δ 7.32 (d, 1H), 7.21 (m, 2H), 6.70 (d, 1H), 5.26 (d, 1H), 5.19 (br s, 1H), 4.80 (br s, 1H), 2.05 (s, 3H), 1.46 (s, 9H), 1.24 (m, 1H), 1.13 (m, 1H), 1.00 (m, 1H), 0.86 (m, 1H).

[00791] Step B: Preparation of *tert*-butyl ((2'S,3'S)-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)carbamate: To a solution of (2'S,3'S)-3'-((tert-butoxycarbonyl)amino)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-yl acetate (55.4 mg, 0.200 mmol) in MeOH (2 mL) was added K_2CO_3 (41.4 mg, 0.300 mmol). The reaction mixture was stirred at ambient temperature for 2 hours, then diluted with 20% iPrOH/80% DCM (10 mL), filtered through a plug of silica, rinsing with 20% iPrOH / 80% DCM (2 x 20 mL). The eluent was concentrated to afford the product as a pale orange solid (55.4 mg, 100% yield).

[00792] Step C: Preparation of (2'S,3'S)-3'-amino-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-ol: To a solution of *tert*-butyl ((2'S,3'S)-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)carbamate (55.4 mg, 0.201 mmol) in iPrOH (1.3 mL) was added HCl (5-6M in iPrOH, 0.2 mL). The reaction mixture was stirred at ambient temperature for 1 hour, and additional HCl (5-6M in iPrOH, 0.2 mL) was added. The reaction mixture was stirred at ambient temperature for 19 hours, and additional HCl (5-6M in iPrOH, 0.2 mL) was added. The reaction mixture was stirred at ambient temperature for 2 hours, then diluted with saturated aqueous NaHCO_3 (25 mL), extracted with 10% MeOH/90% DCM (3 x 25 mL), and the combined organic phases were dried (MgSO_4), filtered, and concentrated to afford the product as a pale blue solid (18.4 mg, 52% yield). ^1H NMR (CD_3OD) δ 7.31 (m, 1H), 7.22 (m, 2H), 6.75 (m, 1H), 4.17 (d, 1H), 3.98 (d, 1H), 1.36 (m, 1H), 1.12 (m, 1H), 0.96 (m, 1H), 0.68 (m, 1H).

Intermediate X11**trans-4'-amino-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-ol**

[00793] Step A: Preparation of 1-methylene-1,2,3,4-tetrahydronaphthalene: To a suspension of methyltriphenylphosphonium bromide (8.797 g, 24.626 mmol) in Et₂O (90 mL) under N₂ was added KOtBu (2.763 g, 24.626 mmol) in several portions over 5 minutes. The reaction mixture was stirred at ambient temperature for 2 hours, then was cooled to 0 °C and a solution of 3,4-dihydronaphthalen-1(2H)-one (2.737 mL, 20.522 mmol) in Et₂O (10 mL) was added. The reaction mixture was allowed to warm to ambient temperature and stirred for 2 hours. The reaction mixture was filtered through Celite® and rinsed with Et₂O (4 x 100 mL), and concentrated. The crude oil was purified by silica column chromatography, eluting with hexanes, to afford the product as a colorless oil (3.02 g, 102% yield). ¹H NMR (CDCl₃) δ 7.64 (m, 1H), 7.16 (m, 2H), 7.09 (m, 1H), 5.47 (dd, 1H), 4.95 (dd, 1H), 2.85 (dd, 2H), 2.55 (m, 2H), 1.88 (m, 2H).

[00794] Step B: Preparation of 3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]: To a solution of diethyl zinc (1M in hexanes, 31.2 mL, 31.2 mmol) and DCM (80 mL), under N₂ flow and cooled to 0 °C, was added a solution of TFA (2.40 mL, 31.204 mmol) in DCM (10 mL) dropwise over 25 minutes. At the end of the addition, DCM (10 mL) was added, and the reaction mixture was stirred at 0 °C for 30 minutes. Diiodomethane (2.51 mL, 31.204 mmol) was added dropwise over 5 minutes, and the reaction mixture was stirred at 0 °C for 1 hour. A solution of 1-methylene-1,2,3,4-tetrahydronaphthalene (3.0 g, 20.803 mmol) in DCM (10 mL) was added dropwise over 5 minutes, then the reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was diluted with H₂O (50 mL), stirred for 30 minutes, then filtered through Celite®, rinsing with DCM (3 x 50 mL). The phases were separated and the aqueous phase extracted with DCM (50 mL). The combined organic phases were dried (MgSO₄), filtered, and partially concentrated afford the product as a yellow oil (12.88 g, 389% yield). The product contained both DCM and CH₂I₂ by ¹H NMR analysis and was used in the next step without further purification. ¹H NMR (CDCl₃) δ 7.04 (m, 3H), 6.66 (d, 1H), 5.30 (s, 5H, CH₂Cl₂), 3.87 (s, 10H, CH₂I₂), 2.88 (dd, 2H), 1.90 (m, 2H), 1.67 (m, 2H), 0.96 (m, 2H), 0.78 (m, 2H).

[00795] Step C: Preparation of 2'H-spiro[cyclopropane-1,1'-naphthalen]-4'(3'H)-one: To a solution of 3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene] (3.29 g, 20.791 mmol) in DCM (100 mL) cooled to 0 °C were added CrO₃ (0.416 g, 4.158 mmol), then *tert*-butyl

hydroperoxide (43.1 mL, 311.9 mmol). The reaction mixture was allowed to warm to ambient temperature slowly and stirred for 24 hours, then the reaction mixture was diluted with MeOH (50 mL) and water (200 mL), then extracted with Et₂O (3 x 150 mL). The combined organic phases were washed with saturated aqueous NaHCO₃ (100 mL) and brine (100 mL), dried (MgSO₄), filtered and concentrated. The crude oil was purified by silica column chromatography, eluting with 0-30% acetone/hexanes, to afford the product as an orange oil (1.68 g, 47% yield). ¹H NMR (CDCl₃) δ 8.04 (dd, 1H), 7.45 (ddd, 1H), 7.25 (m, 1H), 6.83 (dd, 1H), 2.78 (dd, 2H), 1.99 (dd, 2H), 1.10 (m, 2H), 0.99 (m, 2H).

[00796] Step D: Preparation of 3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-4'-ol: To a solution of 2'H-spiro[cyclopropane-1,1'-naphthalen]-4'(3'H)-one (1.68 g, 9.755 mmol) in MeOH (32 mL) cooled to 0 °C was added NaBH₄ (0.443 g, 11.706 mmol) in several portions over 10 min. The reaction mixture was allowed to warm to ambient temperature slowly and stirred for 17 hours. The reaction mixture was diluted with H₂O (100 mL) and extracted with DCM (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO₄), filtered, and concentrated to afford the product as a peachy-orange syrup (927 mg, 55% yield).

[00797] Step E: Preparation of 2'H-spiro[cyclopropane-1,1'-naphthalene]: To a solution of 3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-4'-ol (927 mg, 5.320 mmol) in toluene (17 mL) was added TsOH-H₂O (50.6 mg, 0.266 mmol). The reaction mixture was heated to 110 °C for 90 minutes, then cooled to ambient temperature. The reaction mixture was diluted with H₂O (50 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were dried (MgSO₄), filtered, and concentrated. The crude oil was purified by silica column chromatography, eluting with hexanes, to afford the product as a solution in hexanes and toluene (3.13 g, 377% yield). The product contained both hexanes and toluene by ¹H NMR analysis and was used in the next step without further purification.

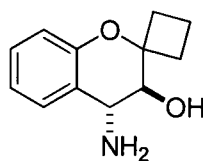
[00798] Step F: Preparation of *trans*-3'-bromo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-4'-ol: To a solution of 2'H-spiro[cyclopropane-1,1'-naphthalene] (100 mg, 0.640 mmol) in DMSO (1.3 mL) were added H₂O (115 μL, 6.401 mmol) then NBS (125 mg, 0.704 mmol). The reaction mixture was stirred at ambient temperature for 21 hours, then was diluted with water (20 mL) and extracted with Et₂O (3 x 20 mL). The combined organic phases were washed with brine (25 mL), dried (MgSO₄), filtered and concentrated. The crude oil was purified by silica column chromatography, eluting with 0-50% acetone/hexanes, to afford the product as a pale yellow residue (13 mg, 8% yield). ¹H NMR (CDCl₃) δ 7.56 (m, 1H), 7.21 (m, 2H), 6.63 (m, 1H), 4.99 (d, 1H), 4.49 (ddd, 1H), 2.62 (br s, 1H), 2.53 (dd, 1H), 2.05 (dd, 1H),

1.22 (m, 1H), 0.94 (m, 2H), 0.86 (m, 1H).

[00799] Step G: Preparation of 2',7b'-dihydro-1a'H-spiro[cyclopropane-1,3'-naphtho[1,2-b]oxirene]: To a solution of *trans*-3'-bromo-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-4'-ol (13 mg, 0.0514 mmol) in Et₂O (2.5 mL) was added KOH (140 mg, 2.495 mmol). The reaction mixture was stirred at ambient temperature for 23 hours, then additional KOH (140 mg, 2.495 mmol) was added. The reaction mixture was stirred at ambient temperature for 3 hours, then was filtered, rinsed with Et₂O, and concentrated to afford the product as a colorless oil (18 mg, 204% yield). The product contained Et₂O by NMR analysis, and was used in the next step without further purification.

[00800] Step H: Preparation of *trans*-4'-amino-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-ol: To a solution of 2',7b'-dihydro-1a'H-spiro[cyclopropane-1,3'-naphtho[1,2-b]oxirene] (8 mg, 0.047 mmol) NH₃ (7N in MeOH, 0.5 mL) was added NH₄OH (0.5 mL). The reaction mixture was heated to 70 °C for 2.5 hours, then cooled to ambient temperature. The reaction mixture was diluted with H₂O (10 mL), acidified with HCl (1 M aqueous, 4 mL), then extracted with Et₂O (10 mL), which was discarded. The aqueous phase was then made basic by addition of aqueous NaOH (4 M aqueous, 0.5 mL), then extracted with 10% MeOH/90% DCM (3 x 10 mL). The combined organic phases were dried (MgSO₄), filtered, concentrated, and dried under high vacuum to afford the product as a beige solid (5.6 mg, 64% yield). ¹H NMR (CDCl₃) δ 7.45 (m, 1H), 7.17 (m, 2H), 6.62 (m, 1H), 3.75 (m, 2H), 2.16 (m, 1H), 1.99 (br s, 3H), 1.64 (m, 1H), 1.18 (m, 1H), 0.90 (m, 2H), 0.81 (m, 1H).

Intermediate X12



trans-4-aminospiro[chroman-2,1'-cyclobutan]-3-ol

[00801] Step A: spiro[chroman-2,1'-cyclobutan]-4-one: To a suspension of 1-(2-hydroxyphenyl)ethanone (3.0 g, 22.035 mmol) in MeOH (37 mL) was added pyrrolidine (3.679 mL, 44.070 mmol). The reaction mixture was stirred at ambient temperature for 15 minutes, and then cyclobutanone (1.65 mL, 22.035 mmol) was added. The reaction mixture was heated to 50 °C for 19 hours, then additional cyclobutanone (1.0 mL) was added and the reaction mixture was heated to 65 °C for 5 days. The reaction mixture was diluted with H₂O (100 mL), extracted DCM (3 x 100 mL), and the combined organic phases were washed with aqueous HCl (1 M, 200 mL), then H₂O (200 mL), then brine (200 mL), dried (MgSO₄), filtered, and concentrated. The crude oil was purified by silica column chromatography, eluting with 0-30% acetone/hexanes, to

afford the product as an orange oil (2.92 mg, 70% yield). ^1H NMR (CDCl_3) δ 7.85 (dd, 1H), 7.47 (ddd, 1H), 6.99 (m, 2H), 2.90 (s, 2H), 2.33 (m, 2H), 2.17 (m, 2H), 1.93 (m, 1H), 1.72 (m, 1H).

[00802] Step B: spiro[chroman-2,1'-cyclobutan]-4-ol: To a solution of spiro[chroman-2,1'-cyclobutan]-4-one (1.00 g, 5.313 mmol) in MeOH (17 mL) cooled to 0 °C was added NaBH_4 (0.241 g, 6.375 mmol) in several portions over 10 minutes. The reaction mixture was allowed to warm to ambient temperature slowly and stirred for 19 hours. The reaction mixture was diluted with H_2O (100 mL) and extracted with DCM (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO_4), filtered, and concentrated to afford the product as a thick yellow syrup (715 mg, 71% yield). ^1H NMR (CDCl_3) δ 7.38 (dd, 1H), 7.17 (ddd, 1H), 6.91 (ddd, 1H), 6.82 (dd, 1H), 4.84 (dd, 1H), 2.35-2.23 (m, 4H), 2.13-2.03 (m, 2H), 1.95-1.85 (m, 1H), 1.78-1.66 (m, 1H).

[00803] Step C: spiro[chromene-2,1'-cyclobutane]: To a solution of spiro[chroman-2,1'-cyclobutan]-4-ol (715 mg, 3.758 mmol) in DCM (7.5 mL) were added molecular sieves (350 mg, 4A, powdered, activated, oven-dried) and MP-TsOH (46 mg, 0.188 mmol). The reaction mixture was stirred at ambient temperature for 4 days, then additional molecular sieves (300 mg, 4A, powdered, activated, oven-dried) and MP-TsOH (46 mg, 0.188 mmol) were added, and the reaction mixture was stirred at ambient temperature for 17 hours. The reaction mixture was filtered, rinsed with DCM, and concentrated. The crude oil was purified by silica column chromatography, eluting with 0-25% acetone/hexanes, to afford the product as a pale yellow oil (135 mg, 21% yield). The product was impure by ^1H NMR analysis and was used in the next step without further purification.

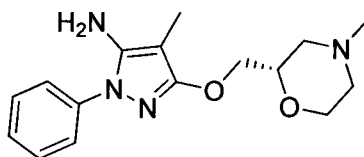
[00804] Step D: trans-3-bromospiro[chroman-2,1'-cyclobutan]-4-ol: To a solution of spiro[chromene-2,1'-cyclobutane] (135 mg, 0.784 mmol) in DMSO (1.5 mL) were added H_2O (141 μL , 7.839 mmol) then NBS (153 mg, 0.862 mmol). The reaction mixture was stirred at ambient temperature for 17 hours, then was diluted with water (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with brine (25 mL), dried (MgSO_4), filtered and concentrated. The crude oil was purified by silica column chromatography, eluting with 0-25% acetone/hexanes, to afford the product as a thick colorless syrup (115 mg, 55% yield). ^1H NMR (CDCl_3) δ 7.37 (dd, 1H), 7.26 (dt, 1H), 7.00 (dd, 1H), 6.94 (dt, 1H), 4.98 (d, 1H), 4.45 (d, 1H), 2.74 (m, 1H), 2.43 (m, 1H), 2.35 (m, 1H), 2.26 (m, 1H), 2.09 (m, 1H), 1.86 (m, 1H).

[00805] Step E: 1a',7b'-dihydrospiro[cyclobutane-1,2'-oxireno[2,3-c]chromene]: To a solution of *trans*-3-bromospiro[chroman-2,1'-cyclobutan]-4-ol (115 mg, 0.427 mmol) in Et_2O

(21 mL) was added KOH (1.2 g, 21.4 mmol). The reaction mixture was stirred at ambient temperature for 19 hours, then was filtered, rinsed with Et₂O, and concentrated to afford the product as a colorless oil (79.8 mg, 99% yield). ¹H NMR (CDCl₃) δ 7.31 (m, 1H), 7.21 (m, 1H), 6.91 (m, 1H), 6.83 (m, 1H), 3.90 (m, 2H), 2.55 (m, 2H), 2.19 (m, 2H), 1.99 (m, 1H), 1.79 (m, 1H).

[00806] Step F: trans-4-aminospiro[chroman-2,1'-cyclobutan]-3-ol: To a hazy solution of 1a',7b'-dihydrospiro[cyclobutane-1,2'-oxireno[2,3-c]chromene] (80 mg, 0.425 mmol) in NH₃ (7N in MeOH, 0.5 mL) was added NH₄OH (1 mL). The reaction mixture was heated to 70 °C for 2 hours, then cooled to ambient temperature. The reaction mixture was diluted with H₂O (10 mL), then extracted with 10% MeOH/90% DCM (2 x 15 mL). The combined organic phases were dried (MgSO₄), filtered, concentrated, and dried under high vacuum to afford the product as a white solid (76 mg, 87% yield). ¹H NMR (CDCl₃) δ 7.35 (m, 1H), 7.16 (m, 1H), 6.94 (m, 1H), 6.84 (m, 1H), 3.79 (d, 1H), 3.54 d, 1H), 2.62 (m, 1H), 2.52 (br s, 2H), 2.31 (m, 2H), 2.02 (m, 2H), 1.83 (m, 1H).

Intermediate Y1



(S)-4-methyl-3-((4-methylmorpholin-2-yl)methoxy)-1-phenyl-1H-pyrazol-5-amine

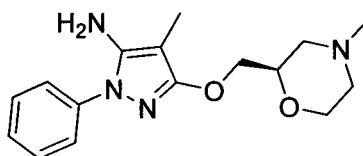
[00807] Step A: Preparation of (S)-tert-butyl 2-(((5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate: A mixture of 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one (Intermediate 2, Step A, 335 mg, 1.77 mmol), (S)-tert-butyl 2-(bromomethyl)morpholine-4-carboxylate (496 mg, 1.77 mmol) and potassium carbonate (612 mg, 4.43 mmol) in dry DMF (15 mL) was heated at 70 °C for 45 hours. The reaction mixture was cooled to ambient temperature and was added to ice-H₂O (10 mL) with dissolving of all of the K₂CO₃. The mixture was extracted with 50% EtOAc/hexanes (3X) and the combined extracts were washed with H₂O (2X) and saturated NaCl. The organic portion was dried over MgSO₄/activated charcoal, eluted through a thin SiO₂ plug (50% EtOAc/hexanes) and concentrated to give the product as a white foam that was dried in vacuum (418 mg, 61%). MS (apci) m/z = 389.3 (M+H).

[00808] Step B: Preparation of (S)-4-methyl-3-(morpholin-2-ylmethoxy)-1-phenyl-1H-pyrazol-5-amine: (S)-tert-butyl 2-(((5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate (332 mg, 0.855 mmol) was dissolved in chilled 5M HCl in iPrOH (10 mL) and the solution was stirred at ambient temperature for 2 hours. The

mixture was concentrated and the residual white solid was washed with Et₂O (2X) and dried. The solid was dissolved in H₂O (5 mL) and 2M NaOH was added to pH=13. The solution was saturated with NaCl(s) and EtOAc (5 mL) was added. The biphasic mixture was stirred for 1 hour, the organic layer removed and the aqueous portion extracted with EtOAc (2X). The combined EtOAc fractions were dried over MgSO₄, filtered and concentrated. The resulting colorless syrup was dried in vacuum to provide the title compound as a white foam (220 mg, 89%). MS (apci) m/z = 289.2 (M+H).

[00809] Step C: (S)-4-methyl-3-((4-methylmorpholin-2-yl)methoxy)-1-phenyl-1H-pyrazol-5-amine: A mixture of (S)-4-methyl-3-(morpholin-2-ylmethoxy)-1-phenyl-1H-pyrazol-5-amine (218 mg, 0.756 mmol) and NaBH(OAc)₃ (506 mg, 2.27 mmol) in 1,2-DCE (4 mL) was cooled to 0 °C and 37% aqueous formaldehyde (62.5 µL, 0.832 mmol) was added. The mixture was stirred for 15 hours during which time the temperature gradually reached ambient. The mixture was treated with chilled 1.0M NaOH (8 mL) and mixed at ambient temperature for 30 minutes. NaCl (s) was added to saturation and the organic layer was removed. The aqueous portion was extracted with CH₂Cl₂ (2X) and the combined organic fractions dried over Na₂SO₄/activated charcoal. The solution was filtered through a SiO₂ plug capped with a layer of MgSO₄ using CH₂Cl₂, EtOAc then 5% (9:1 MeOH/NH₄OH)/EtOAc for elution. The product pool was concentrated to give the title compound as a colorless waxy solid that was dried in vacuum (155 mg, 68%). MS (apci) m/z = 303.2 (M+H).

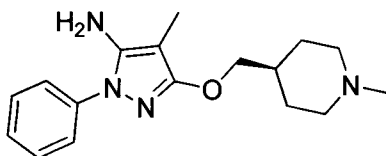
Intermediate Y2



(R)-4-methyl-3-((4-methylmorpholin-2-yl)methoxy)-1-phenyl-1H-pyrazol-5-amine

[00810] Using (R)-*tert*-butyl 2-(bromomethyl)morpholine-4-carboxylate in the procedure described for Intermediate Y1, the title compound was prepared as a white foam (44% over 3 steps). MS (apci) m/z = 303.2 (M+H).

Intermediate Y3

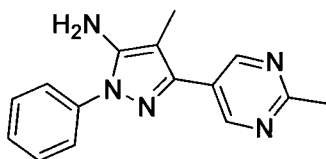


4-methyl-3-((1-methylpiperidin-4-yl)methoxy)-1-phenyl-1H-pyrazol-5-amine

[00811] Using *tert*-butyl 4-(bromomethyl)piperidine-1-carboxylate in the procedure described for Intermediate Y1, the title compound was prepared as a white solid (25% over 3

steps). MS (apci) m/z = 301.2 (M+H).

Intermediate Y4



4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-amine

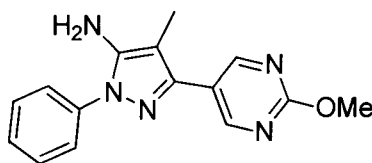
[00812] Step A: Preparation of 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one: A mixture of ethyl 2-cyanopropanoate (50.5 g, 397.2 mmol) and phenylhydrazine (39 mL, 397.2 mmol) in dioxane (100 mL) was heated at 110 °C for 5 days. The cooled mixture was concentrated to 1/2 volume then cooled in ice and triturated with cold Et₂O. The resulting solids were filtered, washed extensively with Et₂O and dried in vacuo to afford 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one (34.69 g, 46% yield) as a fluffy white powder. MS (apci) m/z = 190.1 (M+H).

[00813] Step B: Preparation of 5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl trifluoromethane sulfonate: A suspension of 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one (13.72 g, 72.5 mmol) and N-phenylbis(trifluoromethylsulfonamide) (27.2 g, 76.1 mmol) in DMF (100 mL) was treated with DIEA (37.9 mL, 217.5 mmol) and the mixture stirred at ambient temperature for 16 hours. The mixture was partitioned between saturated NaHCO₃ (400 mL) and EtOAc (200 mL) and the aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic phases were washed with water (5 x 50 mL) and brine (50 mL) then dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica column chromatography eluting with 4:1 hexanes/EtOAc, to afford 5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl trifluoromethane sulfonate (23.1 g, 99% yield) as a pale yellow solid. MS (apci) m/z = 322.0 (M+H).

[00814] Step C: Preparation of 4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-amine: 5-Amino-4-methyl-1-phenyl-1H-pyrazol-3-yl trifluoromethane sulfonate (900 mg, 2.8 mmol), 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (925 mg, 4.2 mmol), K₂CO₃ (1.55 g, 11.2 mmol) and Pd(PPh₃)₄ (324 mg, 0.28 mmol) were combined in toluene (10 mL), water (5 mL) and EtOH (2.5 mL) and warmed to 95 °C in a sealed tube for 16 hours. The cooled mixture was filtered and the filtrate partitioned between water (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic phases were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica column chromatography eluting with 2% MeOH/DCM to afford the title compound (533 mg, 72% yield) as a pink solid. MS (apci) m/z =

266.1 (M+H).

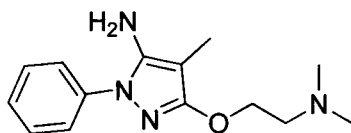
Intermediate Y5



3-(2-methoxypyrimidin-5-yl)-4-methyl-1-phenyl-1H-pyrazol-5-amine

[00815] Prepared according to the procedure for Intermediate Y4, substituting 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine for 2-methoxypyrimidin-5-ylboronic acid in Step C, to afford the title compound (138 mg, 78% yield) as a cream foam. MS (apci) m/z = 282.1 (M+H).

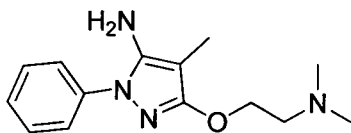
Intermediate Y6



3-(2-(dimethylamino)ethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-amine

[00816] To a thick-walled pressure reaction tube filled with a mixture of 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one (Intermediate 2, Step A, 171 mg, 0.903 mmol), 2-chloro-N,N-dimethylethanamine hydrochloride (130 mg, 0.903 mmol) and Cs₂CO₃ (882 mg, 2.71 mmol) was added DMA (1.8 mL). The white suspension was stirred at ambient temperature for 30 minutes and then at 100 °C overnight. The reaction mixture was partitioned between water and DCM (20 mL each). The phases were separated, and the aqueous phase was extracted with DCM (2 × 10 mL). The combined organic phases were washed with brine (3 × 20 mL), dried (Na₂SO₄), filtered, and concentrated to a dark brownish oil. The crude was purified by silica chromatography (10-20% MeOH/DCM) to yield the product as beige solid (0.13 g, 51% yield). MS (apci) m/z = 261.2 (M+H).

Intermediate Y6

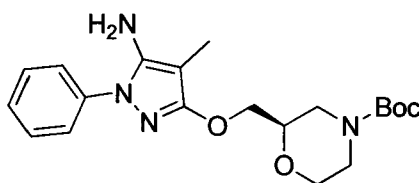


3-(2-(dimethylamino)ethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-amine

[00817] To a thick-walled pressure reaction tube filled with a mixture of 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one (Intermediate 2, Step A, 171 mg, 0.903 mmol), 2-chloro-N,N-dimethylethanamine hydrochloride (130 mg, 0.903 mmol) and Cs₂CO₃ (882 mg, 2.71 mmol) was added DMA (1.8 mL). The white suspension was stirred at ambient

temperature for 30 minutes and then at 100 °C overnight. The reaction mixture was partitioned between water and DCM (20 mL each). The phases were separated, and the aqueous phase was extracted with DCM (2 × 10 mL). The combined organic phases were washed with brine (3 × 20 mL), dried (Na₂SO₄), filtered, and concentrated to a dark brownish oil. The crude was purified by silica chromatography (10-20% MeOH/DCM) to yield the product as beige solid (0.13 g, 51% yield). MS (apci) m/z = 261.2 (M+H).

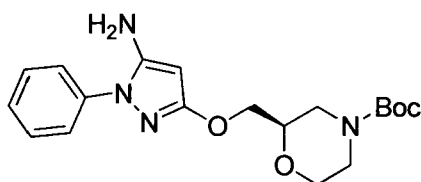
Intermediate Y7



(R)-tert-butyl 2-(((5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate

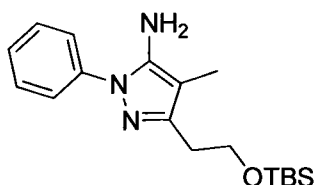
[00818] Step A: Preparation of (R)-tert-butyl 2-(((methylsulfonyl)oxy)methyl)morpholine-4-carboxylate: To a solution of (R)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (2.0 g, 9.205 mmol) and DIEA (2.084 mL, 11.97 mmol) in DCM (46 mL), cooled to 0 °C, was added MsCl (0.819 mL, 10.59 mmol). The reaction mixture was allowed to warm slowly to ambient temperature over 2 hours, then was diluted with H₂O (50 mL), phases separated, and the aqueous phase extracted with DCM (2 x 25 mL). The combined organic phases were washed with brine (50 mL), dried (MgSO₄), filtered, and concentrated to give the product as a pale yellow oil (3.11 g, 114% yield). ¹H NMR (CDCl₃) δ 4.24 (d, 2H), 3.99-3.80 (m, 3H), 3.70 (m, 1H), 3.55 (m, 1H), 3.07 (s, 3H), 2.95 (m, 1H), 2.77 (m, 1H), 1.47 (s, 9H).

[00819] Step B: Preparation of (R)-tert-butyl 2-(((5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate: To 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one (Intermediate 2, Step A, 640 mg, 3.386 mmol) were added DMA (7 mL), Cs₂CO₃ (2.21 g, 6.772 mmol), and (R)-tert-butyl 2-(((methylsulfonyl)oxy)methyl)morpholine-4-carboxylate (1.00 g, 3.386 mmol). The mixture was heated in a sealed pressure tube at 110 °C for 17 hours, then cooled to ambient temperature. The reaction mixture was partitioned between water (40 mL) and DCM (40 mL). The phases were separated, and the aqueous phase was extracted with DCM (2 x 25 mL). The combined organic phases were washed with brine (3 x 50 mL), dried (MgSO₄), filtered, and concentrated. The crude oil was purified by silica column chromatography, eluting with 0-50% acetone/hexanes, to afford the product as a thick amber syrup (871 mg, 66% yield). MS (apci) m/z = 389.2 (M+H).

Intermediate Y8

(R)-tert-butyl 2-(((5-amino-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate

[00820] Prepared according to the procedure of Intermediate Y7, replacing 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one in Step B with 5-amino-1-phenyl-1H-pyrazol-3(2H)-one (Intermediate 203, Step A), to afford the product as a thick amber syrup (489 mg, 39% yield). MS (apci) $m/z = 375.2$ (M+H).

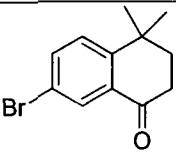
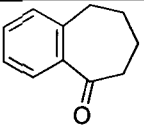
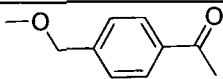
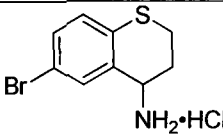
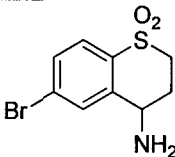
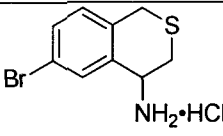
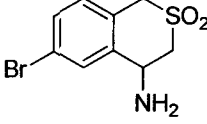
Intermediate Y9

3-(2-(tert-butyldimethylsilyloxy)ethyl)-4-methyl-1-phenyl-1H-pyrazol-5-amine

[00821] To a solution of 2-(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)ethanol (Intermediate P127, 172 mg, 0.792 mmol) in DMF (1 mL) were added TBDMS-Cl (263 mg, 1.74 mmol), then imidazole (135 mg, 1.98 mmol). The reaction mixture was stirred at ambient temperature for 17 hours, then was diluted with H₂O (20 mL) and extracted with DCM (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated to afford the product as a pale brown syrup (249 mg, 95% yield). MS (apci) $m/z = 332.2$ (M+H).

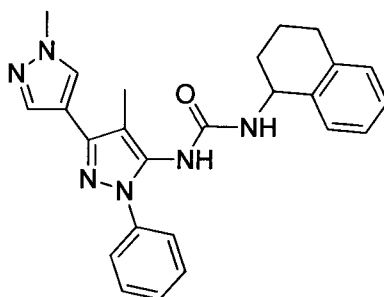
[00822] The table below provides a list of commercially available compounds that were used in the synthesis of intermediates and examples.

Structure	Vendor/Catalog#	CAS#
	Alfa Aesar/AAAL11430-06	447-53-0
	J & W/20-0827S	Not available

Structure	Vendor/Catalog#	CAS#
	CiVenti Chem/CV-1709	166978-46-7
	Aldrich/B10587	826-73-3
	NOVEL Chemical Solutions/AC0320	Not available
	Combi-Blocks, Inc./SS-0260	1170470-60-6
	Activate Scientific/AS2100M500	Not available
	Combi-Blocks, Inc./SS-0277	Not available
	Activate Scientific/AS2096M500	Not available

Preparation of Synthetic Examples

Example 1



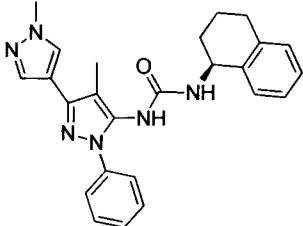
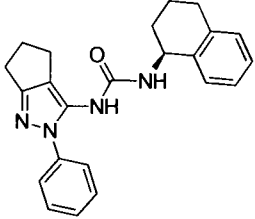
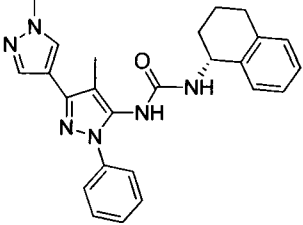
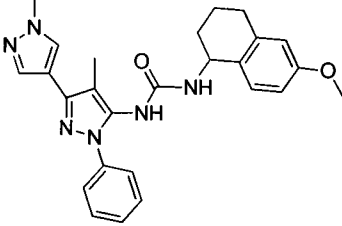
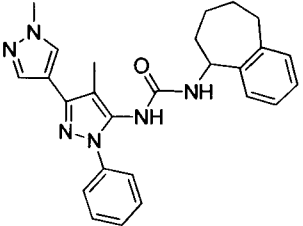
1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(1,2,3,4-tetrahydronaphthalen-1-yl)urea

[00823] 1,2,3,4-tetrahydronaphthalen-1-amine (59.1 mg, 0.402 mmol), phenyl 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-ylcarbamate (Intermediate 13; 100 mg, 0.268 mmol) and DIEA (233 μ L, 1.34 mmol) were combined in 0.2 mL of DMF and stirred at ambient temperature for 1 hour. The mixture was loaded onto a samplet and purified by reverse-phase

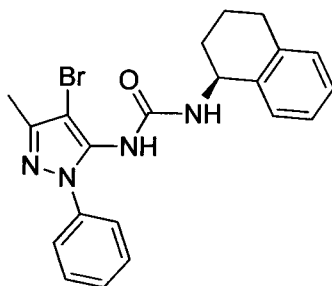
column chromatography, eluting with 10-80% acetonitrile/water, to afford the title compound (71 mg, 0.166 mmol, 62.2 % yield). (MS (apci) m/z = 427.2 (M+H).

[00824] The compounds in Table 2 were prepared by reacting the appropriate amine from Table 1 with the appropriate intermediate phenylcarbamate using the method described for Example 1.

Table 2

Example #	Structure	Name	MS (apci) m/z
2		(S)-1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(1,2,3,4-tetrahydronaphthalen-1-yl)urea	427.2 (M+H)
3		(S)-1-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-3-(1,2,3,4-tetrahydronaphthalen-1-yl)urea	373.2 (M+H)
4		(R)-1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(1,2,3,4-tetrahydronaphthalen-1-yl)urea	427.2 (M+H)
5		1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)urea	457.2 (M+H)
6		1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)urea	441.2 (M+H)

Example #	Structure	Name	MS (apci) m/z
7		1-(chroman-4-yl)-3-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)urea	429.2 (M+H)
8		1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(isochroman-4-yl)urea	429.2 (M+H)
9		1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(2,2-dimethylchroman-4-yl)urea	457.2 (M+H)
10		1-(6-bromoisochroman-4-yl)-3-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea	507.1; 509.1 (M+H)

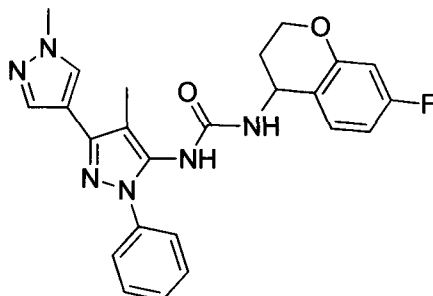
Example 11

(S)-1-(4-bromo-3-methyl-1-phenyl-1H-pyrazol-5-yl)-3-(1,2,3,4-tetrahydronaphthalen-1-yl)urea

[00825] Phenyl (3-methyl-1-phenyl-1H-pyrazol-5-yl)carbamate (Intermediate 1; 40 mg, 0.136 mmol) was dissolved in 1 mL of DCM and N-Bromosuccinimide (29.1 mg, 0.164 mmol) was added. (S)-1,2,3,4-tetrahydronaphthalen-1-amine (30.1 mg, 0.205 mmol) was added followed by DIEA (119 μ L, 0.682 mmol). The reaction was stirred for 2 hours, concentrated and

purified by reverse-phase column chromatography, eluting with 0-90% acetonitrile/water, to afford the title compound (56 mg, 0.132 mmol, 96.5% yield). (MS (apci) m/z = 425.0; 427.0 (M+H).

Example 12



1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(7-fluorochroman-4-yl)urea

[00826] Step A: Preparation of 7-fluorochroman-4-one oxime. 7-fluorochroman-4-one (1.00 g, 6.02 mmol), hydroxylamine hydrochloride (0.627 g, 9.03 mmol) and NaOAc (0.741 g, 9.03 mmol) were combined in EtOH (40 mL) and heated at 100 °C in a sealed vessel overnight. The reaction was filtered through Celite® to afford the title compound as a 0.15M solution in EtOH (40 mL, 6.02 mmol). MS (apci) m/z = 182.1 (M+H).

[00827] Step B: Preparation of 7-fluorochroman-4-amine. Zn dust (1970 mg, 30.1 mmol) was added to 7-fluorochroman-4-one oxime (solution in EtOH, 20056 μ L, 3.01 mmol) and the reaction was stirred at ambient temperature for 4 hours. The reaction was filtered through Celite® and concentrated. The crude product was taken up in 1N HCl (20 ml) and washed with EtOAc (40 mL). The aqueous layer was adjusted to pH >10 with 2N NaOH and extracted with DCM (2x 50 mL). The combined DCM extracts were dried (MgSO₄), filtered and concentrated to provide the title compound (488 mg, 2.92 mmol, 97.0% yield). MS (apci) m/z = 151.1 (M+H-NH₃).

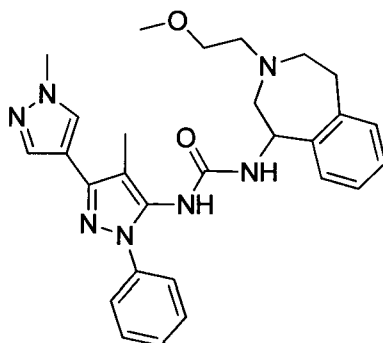
[00828] Step C: Preparation of 1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(7-fluorochroman-4-yl)urea. Phenyl (1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)carbamate (25 mg, 0.0670 mmol), 7-fluorochroman-4-amine (16.8 mg, 0.100 mmol) and DIEA (117 μ L, 0.670 mmol) were combined in 0.2 mL of DMF and stirred ambient temperature for 1 hour. The mixture was loaded onto a samplet and purified by reverse-phase column chromatography, eluting with 0-70% acetonitrile/water, to afford the title compound (19.5 mg, 0.0437 mmol, 65.2% yield). MS (apci) m/z = 447.1 (M+H).

[00829] The compounds in Table 3 were prepared using the appropriate ketone from Table 1 according to the method as described for Example 12 and using the appropriate intermediate phenylcarbamate in Step C.

Table 3

Example #	Structure	Name	MS (apci) m/z
13		1-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-(7-fluorochroman-4-yl)urea	411.2 (M+H)
14		1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(6-fluoro-2-methylchroman-4-yl)urea	461.2 (M+H)
15		1-(7-bromo-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea	503.1; 505.0 (M-H)
16		1-(7-bromo-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea	533.1; 535.1 (M+H)

Example 17



1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(3-(2-methoxyethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepin-1-yl)urea

[00830] Step A: Preparation of 1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(2-oxo-2,3,4,5-tetrahydro-1H-benzo[d]azepin-1-yl)urea. 1-Amino-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (260 mg, 1.47 mmol), phenyl 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-

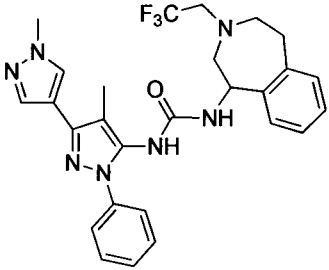
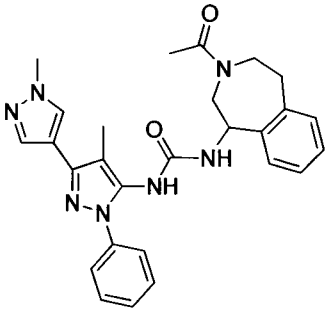
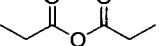
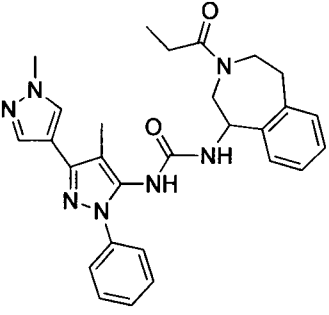
ylcarbamate (Intermediate 13; 500 mg, 1.34 mmol) and DIEA (1166 μ L, 6.70 mmol) were combined in 0.2 mL of DMF and stirred ambient temperature for 2 hours. A thick white slurry formed. Water (2 mL) was added and the white solid was collected, washed with water (1 mL) and DCM (2 x 1 mL) and air-dried to afford the title compound (517 mg, 1.13 mmol, 84.8 % yield). MS (apci) m/z = 456.2 (M+H).

[00831] Step B: Preparation of 1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(2,3,4,5-tetrahydro-1H-benzo[d]azepin-1-yl)urea. 1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(2-oxo-2,3,4,5-tetrahydro-1H-benzo[d]azepin-1-yl)urea (100 mg, 0.2195 mmol) was dissolved in 5 mL of THF and a solution of LAH in THF (548.8 μ L, 0.5488 mmol) was added dropwise. The reaction was stirred at ambient temperature overnight. Additional LAH (548.8 μ L, 0.5488 mmol) was added and the reaction was stirred at ambient temperature for 24 hours. Na₂SO₄.(10 H₂O) (3537 mg, 10.98 mmol) was added and the reaction was stirred for 2 hours, filtered and concentrated. The crude product was by reverse-phase column chromatography, eluting with 0-70% acetonitrile/water, to afford the title compound (40 mg, 0.09059 mmol, 41.27% yield). MS (apci) m/z = 442.2 (M+H).

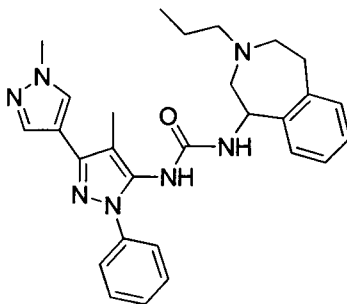
[00832] Step C: Preparation of 1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(3-(2-methoxyethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepin-1-yl)urea. 1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(2,3,4,5-tetrahydro-1H-benzo[d]azepin-1-yl)urea (20.00 mg, 0.04530 mmol), 1-bromo-2-methoxyethane (18.89 mg, 0.1359 mmol) and DIEA (39.45 μ L, 0.2265 mmol) were combined in 0.2 mL of DMF and stirred at ambient temperature overnight. The mixture was loaded onto a samplet and purified by reverse-phase column chromatography, eluting with 0-70 % acetonitrile/water, to afford the title compound (6.3 mg, 0.01261 mmol, 27.84 % yield). MS (apci) m/z = 500.3 (M+H).

[00833] The compounds in Table 4 were prepared using the method as described for Example 17, Step C using the electrophile specified instead of 1-bromo-2-methoxyethane.

Table 4

Ex. #	Electrophile	Structure	Name	MS (apci) m/z
18			1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(3-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepin-1-yl)urea	522.2 (M-H)
19			1-(3-acetyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-1-yl)-3-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)urea	482.2 (M-H)
20			1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(3-propionyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-1-yl)urea	498.2 (M+H)

Example 21

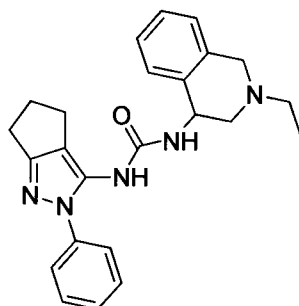


(1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(3-propyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-1-yl)urea

[00834] 1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(2,3,4,5-tetrahydro-1H-benzo[d]azepin-1-yl)urea (15.00 mg, 0.03397 mmol), propionaldehyde (9.866 mg, 0.1699 mmol) and NaBH(OAc)₃ (14.40 mg, 0.06795 mmol) were combined in 1 mL of DCM and

stirred at ambient temperature for 3 days. Additional $\text{NaBH}(\text{OAc})_3$ (14.40 mg, 0.06795 mmol) and 1 mL of THF were added and the reaction was stirred at ambient temperature overnight. NaOH (1N, 1 mL) and DCM (3 mL) were added and the reaction was agitated and filtered through a Phase Separator frit. The organic extract was concentrated and purified by reverse-phase column chromatography, eluting with 0-80% acetonitrile/water, to afford the title compound (1.0 mg, 0.0021 mmol, 6.09% yield). (MS (apci) $m/z = 484.3$ (M+H)).

Example 22



1-(2-ethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea

[00835] Step A: Preparation of 2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid. 1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (530 mg, 2.99 mmol), Boc_2O (685 mg, 3.14 mmol) and NEt_3 (1251 μL , 8.97 mmol) were combined in DCM (20 mL) and stirred at ambient temperature overnight. The reaction was poured into 1N HCl (20 mL), the layers were separated and the aqueous layer was extracted with EtOAc (2x25 mL). The combined organic extracts were dried (MgSO_4) and concentrated to provide the title compound (830 mg, 2.99 mmol, 100 % yield). MS (apci) $m/z = 178.1$ (M+H-Boc).

[00836] Step B: Preparation of tert-butyl 4-(3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)ureido)-3,4-dihydroisoquinoline-2(1H)-carboxylate. 2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (325 mg, 1.17 mmol), NEt_3 (490 μL , 3.52 mmol), and diphenylphosphoryl azide (379 μL , 1.76 mmol) were combined in 2 mL of Toluene in a pressure tube and stirred at 80 °C for 30 minutes. The reaction was cooled and 2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-amine (304 mg, 1.52 mmol) added. The reaction was stirred at 80 °C overnight, cooled, concentrated and purified by reverse-phase column chromatography, eluting with 0-70% acetonitrile/water, to afford the title compound (320 mg, 0.676 mmol, 57.7 % yield). MS (apci) $m/z = 474.2$ (M+H).

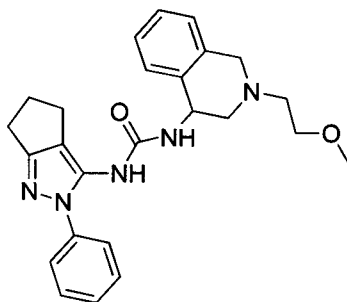
[00837] Step C: Preparation of 1-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-3-(1,2,3,4-tetrahydroisoquinolin-4-yl)urea hydrochloride. Tert-butyl 4-(3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)ureido)-3,4-dihydroisoquinoline-2(1H)-carboxylate (400

mg, 0.845 mmol) and HCl in IPA (507 μ L, 2.53 mmol) were combined in 2 mL of DCM and stirred ambient temperature for 3 days. The mixture was concentrated to afford the title compound (320 mg, 0.781 mmol, 92.4 % yield). MS (apci) m/z = 374.2 (M+H).

[00838] Step D: Preparation of 1-(2-ethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea.

1-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-3-(1,2,3,4-tetrahydroisoquinolin-4-yl)urea hydrochloride (15 mg, 0.037 mmol), iodoethane (17 mg, 0.11 mmol) and DIEA (32 μ L, 0.18 mmol) were combined in 0.2 mL of DMF and stirred ambient temperature overnight. The mixture was loaded onto a samplet and purified by reverse-phase column chromatography, eluting with 0-70 % acetonitrile/water, to afford the title compound (4.0 mg, 0.0100 mmol, 27 % yield. MS (apci) m/z = 402.2 (M+H).

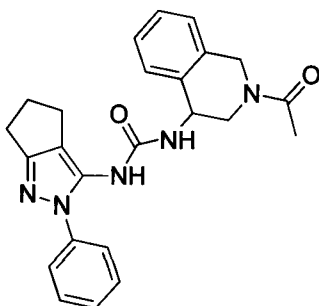
Example 23



1-(2-(2-methoxyethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea

[00839] Prepared by the method as described in Example 28, step D using 1-bromo-2-methoxyethane instead of iodoethane. The material was purified by reverse-phase column chromatography using 0-60% acetonitrile/H₂O as the eluent to provide the title compound (10.1 mg, 0.0234 mmol, 64.0% yield). MS (apci) m/z = 432.2 (M+H).

Example 24

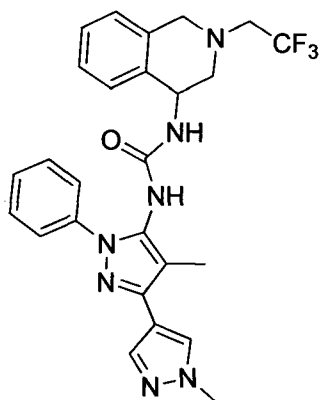


1-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea

[00840] 1-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-3-(1,2,3,4-tetrahydroisoquinolin-4-yl)urea hydrochloride (20 mg, 0.049 mmol), Ac₂O (7.58 μ L, 0.0803

mmol) and NEt_3 (7.46 μL , 0.0536 mmol) were combined in 2 mL of DCM and stirred ambient temperature for 1 hour. NaOH (1N, 3mL) was added and the reaction was extracted with several portions of DCM in a phase separator frit and concentrated to provide the title compound (18.6 mg, 0.0448 mmol, 91.8% yield). MS (apci) m/z = 416.2 (M+H).

Example 25



1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)urea

[00841] Step A: Preparation of 2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-amine.

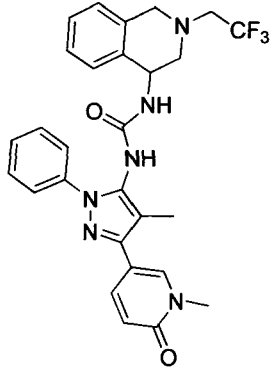
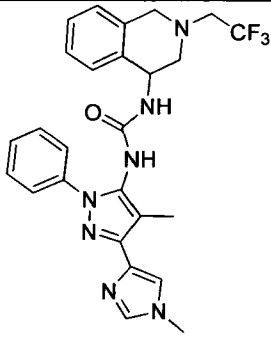
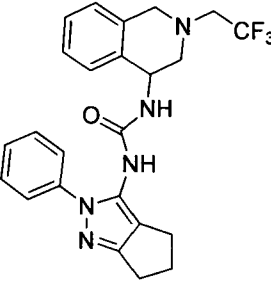
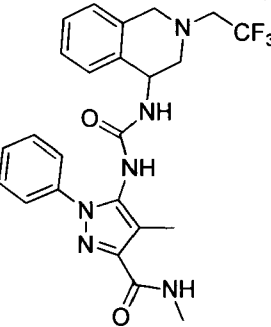
1,2,3,4-tetrahydroisoquinolin-4-amine dihydrochloride (660 mg, 2.98 mmol) was suspended in DMF (5 mL) and NEt_3 (437 μL , 3.13 mmol) added. The mixture was stirred for 4 hours and 2,2,2-trifluoroethyl trifluoromethanesulfonate (693 mg, 2.98 mmol) added. The mixture was stirred for 4 days, quenched with aqueous NaOH (4477 μL , 8.95 mmol) and extracted with several portions of EtOAc. The combined organic extracts were filtered through phase separator paper, concentrated and purified by reverse-phase column chromatography, eluting with 0-60% acetonitrile/water, to afford the title compound (2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-amine (195 mg, 0.847 mmol, 28.4% yield). ^1H NMR (CDCl_3) 7.32-7.39 (m, 1H), 7.15-7.26 (m, 2H), 7.00-7.06 (m, 1H), 3.91-4.04 (m, 2H), 3.78 (d, J = 15 Hz, 1H), 3.14-3.25 (m, 2H), 2.91-3.09 (m, 2H), 1.71 (bs, 2H) ppm.

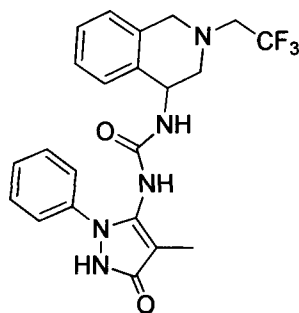
[00842] Step B: Preparation of 1-(1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-yl)-3-(2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)urea.

2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-amine (19 mg, 0.0825 mmol), phenyl 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-ylcarbamate (Intermediate 13; 28.0 mg, 0.0750 mmol) and NEt_3 (31.4 μL , 0.225 mmol) were combined in 0.2 mL of DMF and stirred ambient temperature for 2 hours. The mixture was loaded onto a samplet and purified by reverse-phase column chromatography, eluting with 10-80% acetonitrile/water, to afford the title compound (27.7 mg, 0.0544 mmol, 72.5% yield). MS (apci) m/z = 510.2 (M+H).

[00843] The compounds in Table 5 were prepared using the method described for Example 25, Step C, using the appropriate intermediate phenylcarbamate instead of phenyl 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-ylcarbamate.

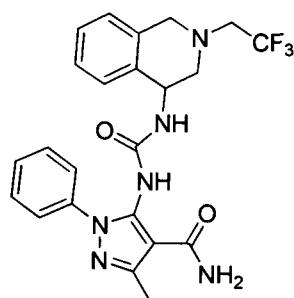
Table 5

Ex. #	Structure	Name	MS (apci) m/z
26		1-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)-3-(2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)urea	535.2 (M+H)
27		1-(4-methyl-3-(1-methyl-1H-imidazol-4-yl)-1-phenyl-1H-pyrazol-5-yl)-3-(2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)urea	510.2 (M+H)
28		1-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-3-(2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)urea	456.2 (M+H)
29		N,4-dimethyl-1-phenyl-5-(3-(2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)ureido)-1H-pyrazole-3-carboxamide	485.2 (M-H)

Example 30

1-(4-methyl-5-oxo-2-phenyl-2,5-dihydro-1H-pyrazol-3-yl)-3-(2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)urea

[00844] CDI (360 mg, 2.22 mmol), 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one (350 mg, 1.85 mmol) and DIEA (805 μ L, 4.62 mmol) were combined in 3 mL of DMF and stirred at ambient temperature overnight. Additional CDI (360 mg, 2.22 mmol) was added and the reaction stirred for 24 hours. A portion of the reaction mixture (365 μ L; 0.182 mmol) was combined with NEt₃ (63.6 μ L, 0.456 mmol) and 2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-amine (35 mg, 0.152 mmol) in 0.1 mL of DMF, and the mixture was stirred ambient temperature for 2 hours. The mixture was loaded onto a samplet and purified by reverse-phase column chromatography using 0-60% acetonitrile/H₂O as the eluent to provide the title compound (59 mg, 0.132 mmol, 87.1% yield). MS (apci) m/z = 446.2 (M+H).

Example 31

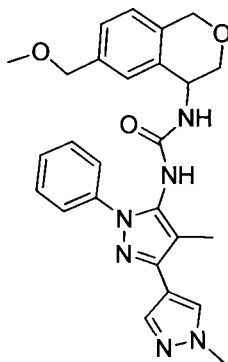
3-methyl-1-phenyl-5-(3-(2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)ureido)-1H-pyrazole-4-carboxamide

[00845] Step A: Preparation of 1-(4-cyano-3-methyl-1-phenyl-1H-pyrazol-5-yl)-3-(2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)urea. 5-amino-3-methyl-1-phenyl-1H-pyrazole-4-carbonitrile (23.7 mg, 0.119 mmol), CDI (22.9 mg, 0.141 mmol) and NEt₃ (45.4 μ L, 0.326 mmol) were combined in 0.2 mL of DMF and stirred ambient temperature overnight. 2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-amine (25 mg, 0.109 mmol) was added and the reaction was stirred at ambient temperature for 2 hours. The mixture was loaded onto a samplet and purified by reverse-phase column chromatography using 0-80% acetonitrile/H₂O as

the eluent to afford the title compound (38 mg, 0.084 mmol, 77.0% yield), which was used immediately in the next step. MS (apci) $m/z = 453.2$ (M-H).

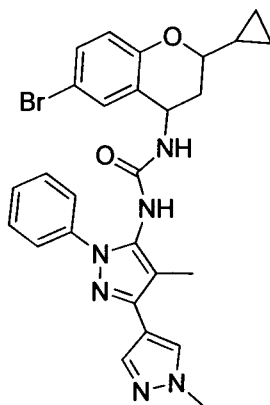
[00846] Step B: Preparation of 3-methyl-1-phenyl-5-(3-(2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)ureido)-1H-pyrazole-4-carboxamide. 1-(4-cyano-3-methyl-1-phenyl-1H-pyrazol-5-yl)-3-(2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)urea (35 mg, 0.07702 mmol), and aqueous concentrated HCl (390.01 mg, 3.8508 mmol) were combined and stirred at ambient temperature for 5 days. The reaction was poured into NaOH (aqueous, 3850.8 μ L, 7.702 mmol) and ice (2 g) and extracted with several portions of 10% IPA/DCM in a phase separator frit. The combined organic extracts were concentrated and purified by reverse-phase column chromatography using 0-80% acetonitrile/H₂O as the eluent to provide the title compound (5.3 mg, 0.0112 mmol, 14.6% yield). MS (apci) $m/z = 471.2$ (M-H).

Example 32



1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(6-(methoxymethyl)isochroman-4-yl)urea

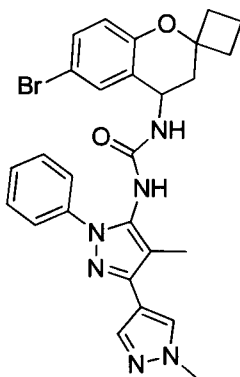
[00847] Potassium methoxymethyltrifluoroborate (12 mg, 0.079 mmol), 1-(6-bromoisochroman-4-yl)-3-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea (20 mg, 0.039 mmol), Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (6.4 mg, 0.0079 mmol) and Cs₂CO₃ (64 mg, 0.20 mmol) were combined in dioxane (2 mL) and water (0.5 mL) in a pressure tube and degassed by bubbling N₂ through the mixture for 10 minutes. The reaction was sealed and heated at 100 °C for 16 hours, cooled, poured into brine (10 mL), and extracted with EtOAc (2 x 10 mL). The combined organic extracts were concentrated and purified by reverse-phase column chromatography using 0-70% acetonitrile/H₂O as the eluent to provide the title compound (9.8 mg, 0.021 mmol, 53% yield). MS (apci) $m/z = 473.2$ (M+H).

Example 33

1-(6-bromo-2-cyclopropylchroman-4-yl)-3-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea

[00848] Step A: Preparation of 6-bromo-2-cyclopropylchroman-4-one. 1-(5-bromo-2-hydroxyphenyl)ethanone (2.0 g, 9.3 mmol), cyclopropanecarbaldehyde (0.78 g, 11 mmol), and pyrrolidine (0.78 mL, 9.3 mmol) were combined in CH₃CN (20 mL), and stirred at ambient temperature for 18 hours. The mixture was concentrated and diluted with diethyl ether (50 mL) and aqueous 1N HCl (20 mL). The phases were separated and the organic phase was washed with aqueous 1N NaOH (20 mL), then brine (200 mL), dried (MgSO₄), filtered, and concentrated. The crude product was purified by silica gel column chromatography using 5-20% EtOAc/hexanes as the eluent to afford the title compound (1.7 g, 6.4 mmol, 68% yield). MS (apci) m/z = 264.9; 266.9 (M-H).

[00849] Step B: Preparation of 1-(6-bromo-2-cyclopropylchroman-4-yl)-3-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea. Prepared using 6-bromo-2-cyclopropylchroman-4-one according to the procedure described in Example 12, Steps A-C. The final compound was purified by reverse-phase column chromatography using 0-80 % acetonitrile/H₂O as the eluent to provide the title compound as a mixture of diastereomers (85 mg, 0.1553 mmol, 23.8% yield for three steps). MS (apci) m/z = 545.1; 547.2 (M-H).

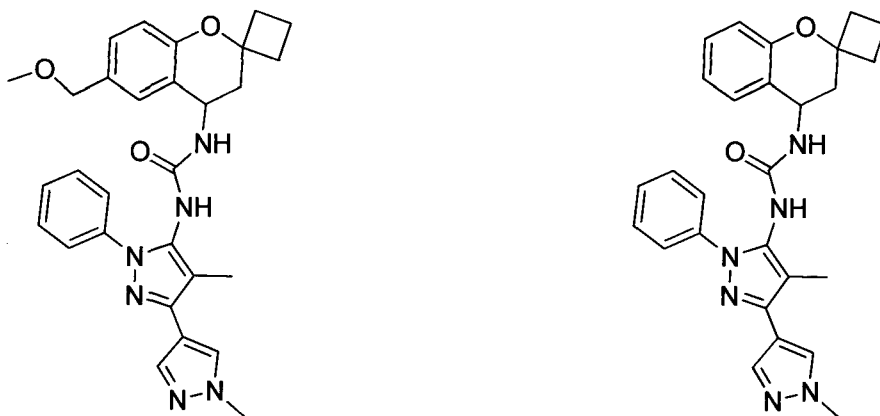
Example 34

1-(6-bromospiro[chroman-2,1'-cyclobutan]-4-yl)-3-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea

[00850] Step A: Preparation of 6-bromospiro[chroman-2,1'-cyclobutan]-4-one. A solution of 1-(5-bromo-2-hydroxyphenyl)ethanone (20 g, 93.00 mmol), cyclobutanone (27.80 mL, 372.0 mmol) and pyrrolidine (8.540 mL, 102.3 mmol) in toluene (150 mL, 93.00 mmol) was heated at reflux overnight. The reaction was partitioned between EtOAc and 2 N HCl, the aqueous layer was washed with EtOAc, and the combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated. The crude product was purified by silica gel column chromatography using 1-15% EtOAc/hexanes as the eluent to afford the title compound (14.04 g, 52.56 mmol, 56.5% yield) as a yellow solid. MS (apci) m/z = 266.0; 268.0 (M⁺).

[00851] Step B: Preparation 1-(6-bromospiro[chroman-2,1'-cyclobutan]-4-yl)-3-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea. Prepared from 6-bromo-2-cyclopropylchroman-4-one according to the procedure described in Example 12, Steps A-C. The final compound was purified by reverse-phase column chromatography using 0-80% acetonitrile/H₂O as the eluent to provide the title compound (99 mg, 0.1808 mmol, 20.0 % yield for three steps). MS (apci) m/z = 545.2; 547.2 (M-H).

Example 35A and 35B



1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(6-(methoxymethyl)spiro[chroman-2,1'-cyclobutan]-4-yl)urea

and

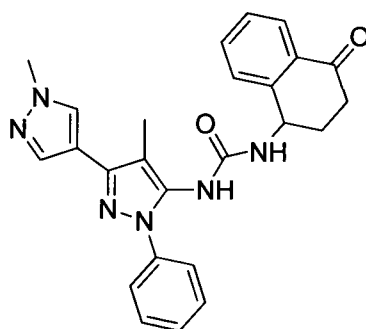
1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(spiro[chroman-2,1'-cyclobutan]-4-yl)urea

[00852] Potassium methoxymethyltrifluoroborate (18 mg, 0.12 mmol), 1-(6-bromospiro[chroman-2,1'-cyclobutan]-4-yl)-3-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea (Example 34; 33 mg, 0.060 mmol), dichloro[1,1'-bis(diphenylphosphino)-ferrocene]palladium (II) dichloromethane adduct (9.8 mg, 0.012 mmol) and Cs₂CO₃ (98 mg,

0.30 mmol) were combined in dioxane (2 mL) and water (0.5 mL) and degassed by bubbling N₂ through the mixture for 10 minutes. The reaction was then sealed in a glass tube and heated at 100 °C for 3 hours. The reaction was cooled, poured into brine (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were concentrated and purified by reverse-phase column chromatography using 0-70% acetonitrile/H₂O as the eluent to provide the title compounds:

1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(6-(methoxymethyl)spiro[chroman-2,1'-cyclobutan]-4-yl)urea [second peak, 2.8 mg, 0.0055 mmol, 9.1% yield, MS (apci) m/z = 513.3 (M+H)] and 1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(spiro[chroman-2,1'-cyclobutan]-4-yl)urea [first peak, 2.50 mg, 0.0053 mmol, 8.8% yield, MS (apci) m/z = 469.2 (M+H)].

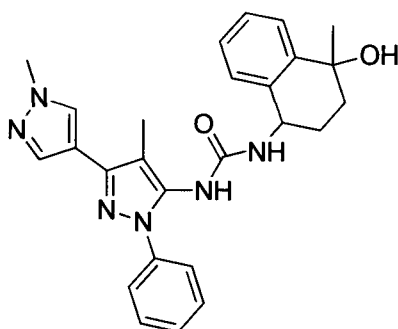
Example 36



1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)urea

[00853] 4-Oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (50 mg, 0.263 mmol), 1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-amine (Intermediate 12; 66.6 mg, 0.263 mmol), NEt₃ (110 µL, 0.789 mmol) and diphenylphosphoryl azide (85.0 µL, 0.394 mmol) were combined in 2 mL of toluene in a sealed pressure tube and stirred at 80 °C overnight. The reaction was cooled, concentrated and purified by reverse-phase column chromatography using 0-60% acetonitrile/H₂O as the eluent to provide the title compound (68 mg, 0.154 mmol, 58.7 % yield). MS (apci) m/z = 441.2 (M+H).

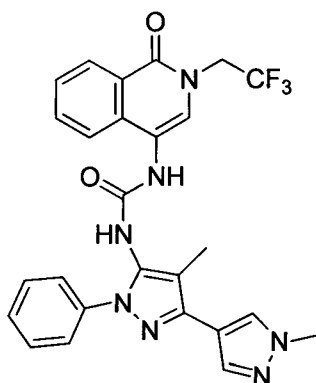
Example 37



1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(4-hydroxy-4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)urea

[00854] 1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)urea (20 mg, 0.0454 mmol) was dissolved in 5 mL of THF and the solution cooled to 0 °C. MeMgBr in THF (81.1 μ L, 0.114 mmol) was added and the reaction was allowed to warm to ambient temperature over 2 hours. Additional MeMgBr in THF (81.1 μ L, 0.114 mmol) was added and the reaction stirred at ambient temperature for 1 hours. The reaction was quenched with water and extracted with several portions of EtOAc. The combined organic extracts were filtered through phase separator paper, concentrated and purified by silica gel column chromatography using 5-100% acetone/hexanes as the eluent to afford the title compound (4.4 mg, 0.00964 mmol, 21.2% yield). MS (apci) m/z = 457.2 (M+H).

Example 38



1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(1-oxo-2-(2,2,2-trifluoroethyl)-1,2-dihydroisoquinolin-4-yl)urea

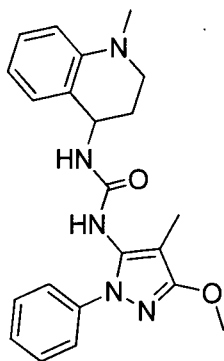
[00855] Step A: Preparation of 4-nitro-2-(2,2,2-trifluoroethyl)isoquinolin-1(2H)-one. 4-Nitroisoquinolin-1(2H)-one (50 mg, 0.26 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (79 mg, 0.34 mmol) and K_2CO_3 (182 mg, 1.3 mmol) were combined in 0.2 mL of DMF and stirred at ambient temperature for 2 hours. The mixture was filtered, loaded onto a samplet, and purified by reverse-phase column chromatography eluting with 0-80% acetonitrile/water to afford the title compound (63 mg, 0.23 mmol, 88 % yield) as a white solid. 1H NMR ($CDCl_3$) 8.66-8.71 (m, 1H), 8.57 (s, 1H), 8.49-8.54 (m, 1H), 7.87-7.94 (m, 1H), 7.66-7.72 (m, 1H), 4.73-4.82 (m, 2H).

[00856] Step B: Preparation of 4-amino-2-(2,2,2-trifluoroethyl)isoquinolin-1(2H)-one. 4-nitro-2-(2,2,2-trifluoroethyl)isoquinolin-1(2H)-one (5.00 mg, 0.0184 mmol) was dissolved in MeOH (0.5 mL) and aqueous saturated NH_4Cl (0.2 mL) was added followed by Zn dust (6.01 mg, 0.0919 mmol). The reaction was stirred at ambient temperature overnight, filtered, and extracted with several portions of DCM in a phase separator frit. The combined DCM extracts

were concentrated to provide the title compound (4.00 mg, 0.0165 mmol, 89.9 % yield). MS (apci) m/z = 243.1 (M+H).

[00857] Step C: Preparation of 1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(1-oxo-2-(2,2,2-trifluoroethyl)-1,2-dihydroisoquinolin-4-yl)urea. 4-Amino-2-(2,2,2-trifluoroethyl)isoquinolin-1(2H)-one (2.60 mg, 0.0107 mmol), phenyl (1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)carbamate (4.01 mg, 0.0107 mmol) and NEt_3 (4.49 μL , 0.0322 mmol) were combined in 0.2 mL of DMF and stirred at ambient temperature for 2 hours. The mixture was loaded onto a samplet and purified by reverse-phase column chromatography, eluting with 0-70% acetonitrile/water, to afford the title compound (2.63 mg, 0.00504 mmol, 47.0% yield). MS (apci) m/z = 522.2 (M+H).

Example 39



1-(3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-(1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)urea

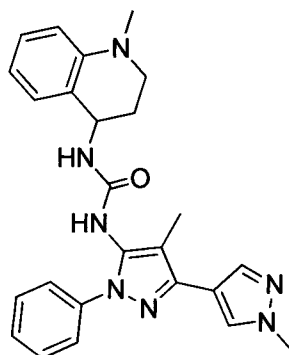
[00858] Step A: Preparation of tert-butyl (1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate: To a solution of tert-butyl (1,2,3,4-tetrahydroquinolin-4-yl)carbamate (250 mg, 1.01 mmol) and DIEA (526 μL , 3.02 mmol) in dry DMF (2.0 mL) was added methyl iodide (66.1 μL , 1.06 mmol). The mixture was stirred at ambient temperature for 7 hours. Additional methyl iodide (33 μL) was added and the mixture was stirred for an additional 16 hours. The mixture was diluted with H_2O (6 mL) and extracted with Et_2O (3X). The combined extracts were washed with H_2O (2x) and Brine, dried (MgSO_4) and filtered through a SiO_2 plug (Et_2O elution). The eluent was concentrated and the residual colorless syrup was purified on a SiO_2 column (CH_2Cl_2 elution) to provide the title compound as a colorless film (150 mg, 57% yield). ^1H NMR (CDCl_3) δ 7.16 (dd, J =18.4, 8.7 Hz, 2H), 6.66 (t, J =7.4 Hz, 1H), 6.61 (d, J =8.3 Hz, 1H), 4.78 (br s, 1H), 4.74 (br s, 1H), 3.21 (t, J =5.7 Hz, 2H), 2.90 (s, 3H), 2.06, (m, 2H), 1.47 (s, 9H) ppm.

[00859] Step B: Preparation of 1-methyl-1,2,3,4-tetrahydroquinolin-4-amine dihydrochloride: To a solution of tert-butyl (1-methyl-1,2,3,4-tetrahydroquinolin-4-

yl)carbamate (145 mg, 0.553 mmol) in EtOAc (4 mL) was added 4M HCl (2.07 mL, 8.29 mmol) in dioxane and the mixture was stirred at ambient temperature for 2.5 hours. The resulting white suspension was diluted with Et₂O (6 mL) and the solid collected via vacuum filtration. The solid was washed with Et₂O and dried under vacuum to afford the title compound as a white solid (100 mg, 77% yield). ¹H NMR (CD₃OD) δ 7.47-7.38 (m, 2H), 7.18-7.05 (m, 2H), 4.62 (unresolved, 1H), 3.60-3.48 (m, 2H), 3.13 (s, 3H), 2.51-2.41 (m, 1H), 2.33-2.24 (m, 1H) ppm.

[00860] Step C: Preparation of 1-(3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-(1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)urea: To a mixture of phenyl (3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)carbamate (32.3 mg, 0.100 mmol) and 1-methyl-1,2,3,4-tetrahydroquinolin-4-amine dihydrochloride (28.2 mg, 0.120 mmol) in dry CH₂Cl₂ (0.4 mL) was added DIEA (69.7 μL, 0.400 mmol) and the resulting solution was stirred at ambient temperature for 5 hours. The reaction mixture was diluted with CH₂Cl₂ (3 mL) and washed sequentially with H₂O, 1M NaOH (2X) and H₂O. The organic phase was dried (Na₂SO₄) and passed through a short SiO₂ column eluting with CH₂Cl₂, then 50% EtOAc-hexanes. The 50% EtOAc-hexanes pool was concentrated and the residual white solid was dried under vacuum to provide the title compound (34 mg, 87% yield). ¹H NMR (DMSO₆) δ 7.81 (s, 1H), 7.49 (d, J=8.3 Hz, 2H), 7.43 (t, J=7.3 Hz, 2H), 7.26 (t, J=7.3 Hz, 1H), 7.07 (t, J=7.4 Hz, 1H), 6.97 (d, J=8.2 Hz, 1H), 6.66 (d, J=8.2 Hz, 1H), 6.59 (app. dd, J=12.8, 7.4 Hz, 2H), 4.71 (dd, J=13.5, 5.6 Hz, 1H), 3.86 (s, 3H), 3.23-3.10 (m, 2H), 2.83 (s, 3H), 1.94-1.81 (m, 2H), 1.78 (s, 3H) ppm.

Example 40

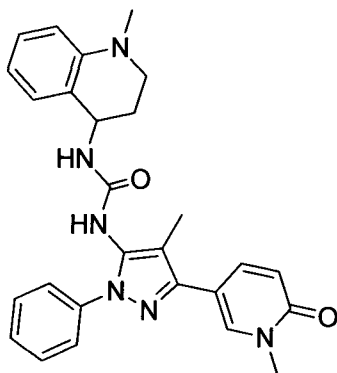


1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)urea

[00861] To a mixture of phenyl (1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)carbamate (Intermediate 13; 37.3 mg, 0.100 mmol) and 1-methyl-1,2,3,4-tetrahydroquinolin-4-amine dihydrochloride (28.2 mg, 0.120 mmol) in dry CH₂Cl₂ (0.4 mL) was added DIEA (69.7 μL, 0.400 mmol) and the resulting solution was stirred at ambient temperature for 5 hours. The reaction mixture was diluted with CH₂Cl₂ (3 mL) and washed sequentially with H₂O, 1M NaOH

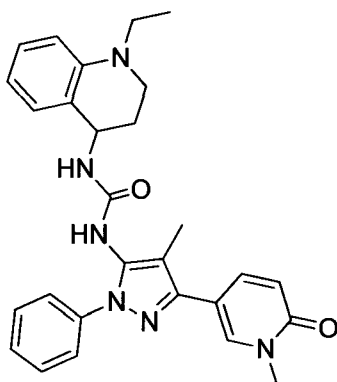
(2x) and H₂O. The organic phase was dried (Na₂SO₄) and passed through a short SiO₂ column eluting with CH₂Cl₂, 50% EtOAc-hexanes, then EtOAc. The EtOAc pool was concentrated and the residual white solid dried under vacuum to furnish the title compound (42 mg, 95% yield). MS (apci) m/z = 442.2 (M+H).

Example 41



1-(1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)urea

[00862] To a mixture of phenyl (4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)carbamate (Intermediate 8; 20.0 mg, 0.050 mmol) and 1-methyl-1,2,3,4-tetrahydroquinolin-4-amine dihydrochloride (14.1 mg, 0.060 mmol) in dry CH₂Cl₂ (0.4 mL) was added DIEA (34.8 μ L, 0.200 mmol) and the resulting solution was stirred at ambient temperature for 4.5 hours. The reaction mixture was diluted with CH₂Cl₂ (2 mL) and washed sequentially with H₂O, 1M NaOH (2x) and H₂O. The organic phase was dried (Na₂SO₄) and passed through a short SiO₂ column eluting with CH₂Cl₂, EtOAc then 5% MeOH/EtOAc. The 5% MeOH/EtOAc pool was concentrated and the residual solid washed with Et₂O and dried under vacuum to furnish the title compound as a white solid (17 mg, 73% yield). MS (apci) m/z = 467.2 (M-H).

Example 42

1-(1-ethyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)urea

[00863] Step A: Preparation of tert-butyl (1-ethyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate:

To a solution of tert-butyl (1,2,3,4-tetrahydroquinolin-4-yl)carbamate (250 mg, 1.01 mmol) and DIEA (526 μ L, 3.02 mmol) in dry DMF (2.0 mL) was added ethyl iodide (121 μ L, 1.50 mmol) and the mixture was stirred at ambient temperature for 5 hours. The mixture was heated at 50 °C for 16 hours and additional ethyl iodide (50.0 μ L) was added. The mixture was heated at 70 °C for 5 hours and was cooled to ambient temperature. The mixture was diluted with H₂O (12 mL) and extracted with Et₂O (3x). The combined extracts were washed with H₂O (2x) and Brine, dried (MgSO₄) and filtered through a SiO₂ plug (Et₂O elution). The eluent was concentrated and the residual colorless syrup was dried under vacuum to provide the title compound (264 mg, 95 % yield). ¹H NMR (CDCl₃) δ 7.17 (d, J=7.5 Hz, 1H), 7.12 (t, J=7.6 Hz, 1H), 6.61 (t, J=7.5 Hz, 2H), 4.73 (unresolved, 2H), 3.44-3.28 (m, 2H), 3.28-3.17 (m, 2H), 2.06-1.99 (m, 2H), 1.47 (s, 9H), 1.13 (t, J=7.1 Hz, 3H) ppm.

[00864] Step B: Preparation of 1-ethyl-1,2,3,4-tetrahydroquinolin-4-amine dihydrochloride:

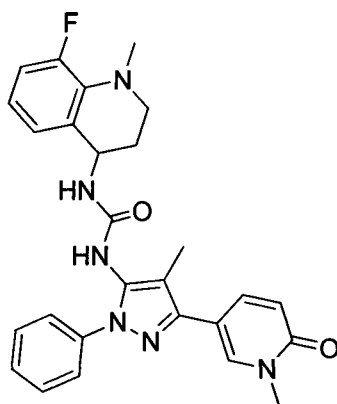
To a solution of tert-butyl (1-ethyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (264 mg, 0.955 mmol) in EtOAc (3 mL) was added 4M HCl (3.58 mL, 14.3 mmol) in dioxane and the mixture was stirred at ambient temperature for 2 hours. The resulting white suspension was diluted with Et₂O (8 mL) and the solid collected via vacuum filtration. The solid was washed with Et₂O and dried under vacuum to afford the title compound as a white solid (222 mg, 93 % yield). ¹H NMR (CD₃OD) δ 7.68-7.59 (m, 1H), 7.57-7.50 (m, 1H), 7.47-7.36 (m, 2H), 4.78-4.72 (m, 1H), 3.80-3.60 (m, 4H), 2.67-2.56 (m, 1H), 2.41-2.30 (m, 1H), 1.40 (m, 3H) ppm.

[00865] Step C: Preparation of 1-(1-ethyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)urea:

The title compound was prepared utilizing 1-ethyl-1,2,3,4-tetrahydroquinolin-4-amine dihydrochloride instead of 1-methyl-1,2,3,4-tetrahydroquinolin-4-amine dihydrochloride according to the procedure describe

in Example 41. The compound was isolated as a white solid (25.0 mg, 83 % yield). MS (apci) $m/z = 483.2$ (M+H).

Example 43



1-(8-fluoro-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)urea

[00866] Step A: Preparation of 8-fluoro-2,3-dihydroquinolin-4(1H)-one oxime: To a mixture of 8-fluoro-2,3-dihydroquinolin-4(1H)-one (300 mg, 1.82 mmol) and hydroxylamine hydrochloride (379 mg, 5.45 mmol) in absolute EtOH (18 mL) was added pyridine (294 μ L, 3.63 mmol) and the mixture was heated at reflux for 16 hours. The mixture was cooled to ambient temperature and concentrated. The residual oily solid was treated with H₂O and the mixture extracted with CH₂Cl₂ (3x). The combined organic extracts were washed with H₂O, dried over Na₂SO₄ and passed through a SiO₂ plug (eluting with CH₂Cl₂ and then 25% EtOAc-hexanes for elution). The eluent was concentrated to give a cloudy film that was washed with hexanes and dried under vacuum to provide the title compound as a white solid (245 mg, 75 % yield). MS (apci) $m/z = 181.1$ (M+H).

[00867] Step B: Preparation of 8-fluoro-1,2,3,4-tetrahydroquinolin-4-amine: A solution of 8-fluoro-2,3-dihydroquinolin-4(1H)-one oxime (225 mg, 1.25 mmol) in MeOH (5 mL) was cooled to 0 °C and Zn dust (<10 micron, 408.2 mg, 6.24 mmol) was added in one portion. Saturated NH₄Cl (1.0 mL) was added over 2 minutes and the mixture was stirred for 5 minutes. The mixture was allowed to reach ambient temperature and was stirred for 6 hours. The mixture was filtered through packed Celite® (MeOH for rinse and elution) and concentrated to a colorless syrup. The syrup was treated with 1M K₂CO₃ (5 mL) and extracted with EtOAc (3x). The combined extracts were dried over MgSO₄, filtered through packed Celite® and concentrated to provide the title compound as a colorless syrup that was dried under vacuum (183 mg, 88 % yield). ¹H NMR (CDCl₃) δ 6.99 (d, J=7.4 Hz, 1H), 6.84 (dd, J=11.3, 8.0 Hz, 1H), 6.56 (app dt, J=8.0, 5.2 Hz, 1H), 4.14 (br s, 1H), 4.03 (t, J=4.8 Hz, 1H), 3.46-3.33 (m, 2H), 2.06-1.98 (m, 1H), 1.88-1.81 (m, 1H), 1.56 (br s, 2H) ppm.

[00868] Step C: Preparation of tert-butyl (8-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)carbamate:

A solution of 8-fluoro-1,2,3,4-tetrahydroquinolin-4-amine (180 mg, 1.08 mmol) in THF (3 mL) was cooled to 0 °C and Boc₂O (244 mg, 1.08 mmol) was added in one portion. The mixture was stirred for 15 minutes then at ambient temperature for 2 hours. The mixture was concentrated to a colorless syrup that was dried under vacuum for 16 hours. The syrup was dissolved in Et₂O and eluted through a SiO₂ plug eluting with Et₂O. The eluent was concentrated and the residual colorless film was dried under vacuum to provide the title compound as a white foam (289 mg, 100% yield). ¹H NMR (CDCl₃) δ 6.98 (d, J=7.7 Hz, 1H), 6.86 (dd, J=11.0, 8.0 Hz, 1H), 6.56 (app dt, J=7.9, 5.3 Hz, 1H), 4.84 (unresolved, 1H), 4.74 (unresolved, 1H), 4.13 (br s, 1H), 3.43-3.36 (m, 1H), 3.34-2.26 (m, 1H), 2.05 (q, J=5.4 Hz, 2H), 1.47 (s, 9H) ppm.

[00869] Step D: Preparation of tert-butyl (8-fluoro-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate:

To a solution of tert-butyl (8-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (288 mg, 1.08 mmol) and DIEA (565 μL, 3.24 mmol) in dry DMA (4 mL) was added methyl iodide (101 μL, 1.62 mmol) and the mixture stirred at ambient temperature for 5 hours. Additional methyl iodide (101 μL, 1.62 mmol) was added and the mixture heated at 50 °C for 6 hours. The reaction mixture was cooled to ambient temperature and was diluted with H₂O (25 mL). The mixture was extracted with Et₂O (3x) and the combined organic extracts were washed with H₂O (2x) and saturated NaCl. The organic portion was dried over MgSO₄/activated carbon and eluted through a SiO₂ plug (Et₂O elution). The eluent was concentrated to provide the title compound as a white solid after drying under vacuum (100 mg, 33% yield). ¹H NMR (CDCl₃) δ 7.00 (d, J=7.7 Hz, 1H), 6.89 (dd, J=11.0, 8.0 Hz, 1H), 6.68 (app dt, J=7.9, 5.3 Hz, 1H), 4.84 (unresolved, 1H), 4.74 (br s, 2H), 3.18-3.08 (m, 2H), 2.98 (s, 3H), 2.06-1.95 (m, 2H), 1.47 (s, 9H) ppm.

[00870] Step E: Preparation of 8-fluoro-1-methyl-1,2,3,4-tetrahydroquinolin-4-amine dihydrochloride:

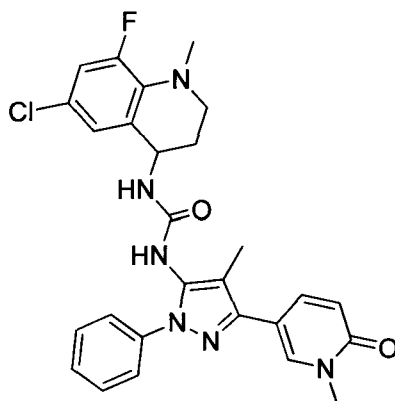
To a solution of tert-butyl (8-fluoro-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (45.0 mg, 0.161 mmol) in EtOAc (0.6 mL) was added 4M HCl (602 μL, 2.41 mmol) in dioxane and the mixture was stirred at ambient temperature for 3 hours. The resulting white suspension was diluted with Et₂O (5 mL) and the solid collected via vacuum filtration. The solid was washed with Et₂O and dried under vacuum to afford the title compound as an ivory white solid (39 mg, 96% yield). MS (apci) m/z = 181.1 (M+H).

[00871] Step F: 1-(8-fluoro-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)urea:

The title compound was prepared utilizing 8-fluoro-1-methyl-1,2,3,4-tetrahydroquinolin-4-amine dihydrochloride instead of 1-methyl-1,2,3,4-tetrahydroquinolin-4-amine dihydrochloride in the preparation outlined for

Example 41. The compound was isolated as a white solid (18 mg, 59 % yield). MS (apci) m/z = 487.2 (M+H).

Example 44



1-(6-chloro-8-fluoro-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)urea

[00872] Step A: Preparation of tert-butyl (6-chloro-8-fluoro-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate: A solution of tert-butyl (8-fluoro-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (45.0 mg, 0.160 mmol) in CH₃CN (1.6 mL) was cooled to 0 °C and N-chlorosuccinimide (23.6 mg, 0.177 mmol) was added in one portion. The mixture was stirred for 4 hours during which time the temperature rose to ambient after 1 hour. The mixture was treated with pyridin-1-ium 4-methylbenzenesulfonate (PPTS) (4.03 mg, 0.016 mmol) and was heated at 45 °C for 20 hours. The reaction mixture was added to half-saturated NaHCO₃ (4 mL) and mixed. The mixture was extracted with CH₂Cl₂ (3x) and the combined extracts washed with H₂O (2x) and dried over Na₂SO₄/activated carbon. The dried solution was filtered through a SiO₂ plug (CH₂Cl₂ elution) and concentrated. The residue was dried under vacuum to afford the title compound as a light yellow solid (30 mg, 59% yield). MS (apci) m/z = 315.1 (M+H).

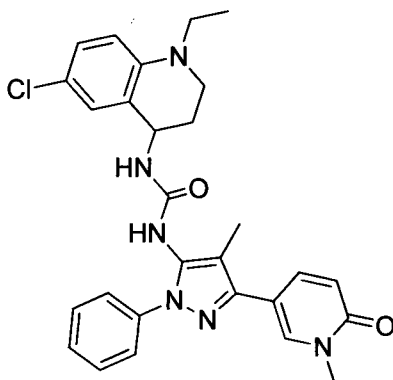
[00873] Step B: Preparation of 6-chloro-8-fluoro-1-methyl-1,2,3,4-tetrahydroquinolin-4-amine dihydrochloride: To a solution of tert-butyl (6-chloro-8-fluoro-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (29.0 mg, 0.083 mmol) in EtOAc (1.0 mL) was added 4M HCl (1.04 μ L, 4.15 mmol) in dioxane and the mixture was stirred at ambient temperature for 16 hours. The resulting white suspension was diluted with Et₂O (5 mL) and the solid collected via vacuum filtration. The solid was washed with Et₂O and dried under vacuum to afford the title compound as a white solid (18 mg, 75% yield). ¹H NMR (CD₃OD) δ 7.19-7.14 (m, 2H), 4.51 (m, 1H), 3.31 (s, 3H), 3.10-3.08 (m, 2H), 2.29-2.19 (m, 1H), 2.18-2.09 (m, 1H) ppm.

[00874] Step C: Preparation of 1-(6-chloro-8-fluoro-1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)urea:

Prepared according to the method of Example 41, using 6-chloro-8-fluoro-1-methyl-1,2,3,4-

tetrahydroquinolin-4-amine dihydrochloride instead of 1-methyl-1,2,3,4-tetrahydroquinolin-4-amine dihydrochloride. The title compound was obtained as a white solid (16 mg, 56% yield). MS (apci) m/z = 519.2 (M-H).

Example 45



1-(6-chloro-1-ethyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)urea

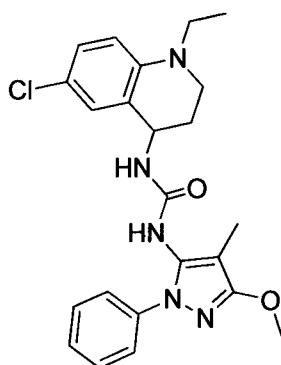
[00875] Step A: Preparation of tert-butyl (6-chloro-1-ethyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate: A solution of tert-butyl (1-ethyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (165 mg, 0.597 mmol) in dry CH₃CN (3 mL) was cooled to 0 °C and N-chlorosuccinimide (85.4 mg, 0.627 mmol) was added in one portion. The mixture was stirred for 6 hours during which time the temperature rose to ambient after 1 hour. The reaction mixture was treated with saturated NaHCO₃ (4 mL) and H₂O (4 mL) and mixed. The mixture was extracted with Et₂O (3X) and the combined extracts were washed with H₂O (2x), saturated NaCl and dried over MgSO₄/activated carbon. The dried solution was filtered through a SiO₂ plug (Et₂O elution) and concentrated. The residue was purified on a SiO₂ column (25%, 50%, 100% CH₂Cl₂-hexanes step gradient) to provide the title compound as a white solid (70 mg, 38% yield). ¹H NMR (CDCl₃) δ 7.13 (s, 1H), 7.05 (d, J=8.8 Hz, 1H), 6.52 (d, J=8.8 Hz, 1H), 4.70 (unresolved, 2H), 3.42-3.24 (m, 2H), 3.23 (dd, J=5.4, 5.4 Hz, 2H), 2.01 (dd, J=10.6, 4.7 Hz, 2H), 1.48 (s, 9H), 1.12 (t, J=7.1 Hz, 3H) ppm.

[00876] Step B: Preparation of 6-chloro-1-ethyl-1,2,3,4-tetrahydroquinolin-4-amine dihydrochloride: To a solution of tert-butyl (6-chloro-1-ethyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (69.0 mg, 0.220 mmol) in dry EtOAc (2.0 mL) was added 4M HCl (1.67 mL, 6.68 mmol) in dioxane and the mixture was stirred at ambient temperature for 4 hours. The mixture was treated with additional 4M HCl (1.67 mL, 6.68 mmol) in dioxane and MeOH (0.5 mL) and stirred for 1 hour. The mixture was concentrated to a clear glass that was treated with Et₂O and agitated until fine white suspension formed. The solid was allowed to settle, the solvent decanted and the residual solid washed with Et₂O (2x). The solid was dried under vacuum to

furnish the title compound as a white solid (56 mg, 89% yield). MS (apci) m/z = 194.1 (M-NH₂).

[00877] Step C: Preparation of 1-(6-chloro-1-ethyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)urea: The title compound was prepared utilizing 6-chloro-1-ethyl-1,2,3,4-tetrahydroquinolin-4-amine dihydrochloride instead of 1-methyl-1,2,3,4-tetrahydroquinolin-4-amine dihydrochloride in the preparation outlined for Example 41. The compound was isolated as a white solid (16 mg, 62 % yield). MS (apci) m/z = 515.2 (M-H).

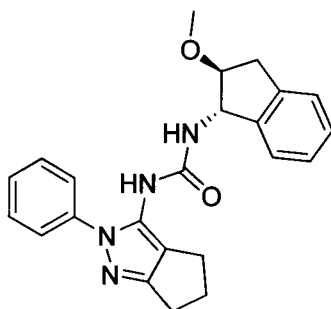
Example 46



1-(6-chloro-1-ethyl-1,2,3,4-tetrahydroquinolin-4-yl)-3-(3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea

[00878] The title compound was prepared utilizing 6-chloro-1-ethyl-1,2,3,4-tetrahydroquinolin-4-amine dihydrochloride instead of 1-methyl-1,2,3,4-tetrahydroquinolin-4-amine dihydrochloride of in the preparation outlined for Example 39, Step C. The compound was isolated as a white solid (20 mg, 98% yield). MS (apci) m/z = 440.1 (M+H).

Example 47



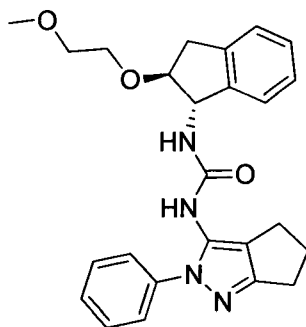
1-((1S,2S)-2-methoxy-2,3-dihydro-1H-inden-1-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea

[00879] Step A: Preparation of tert-butyl ((1S,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamate: To a turbid suspension of (1S,2S)-1-amino-2,3-dihydro-1H-inden-2-ol (140 mg, 0.938 mmol) in DCM (4.7 mL, 0.938 mmol) was added triethylamine (262 μ L, 1.88 mmol),

followed by Boc_2O (215 mg, 0.985 mmol) in one portion at ambient temperature. The reaction was stirred for 2 days, filtered (GF/F paper), rinsed with DCM and concentrated. The crude product was purified by silica gel chromatography (3:1 hexanes/EtOAc) to yield the product as white solid (200 mg, 86% yield). ^1H NMR (CDCl_3) δ 7.20-7.26 (m, 4 H), 5.05 (br s, 1 H), 4.88-4.92 (m, 1 H), 4.38-4.45 (m, 1 H), 4.29 (br s, 1 H), 3.25-3.31 (m, 1 H), 2.88-2.94 (m, 1 H), 1.50 (s, 9 H) ppm.

[00880] Step B: Preparation of tert-butyl ((1*S*,2*S*)-2-methoxy-2,3-dihydro-1*H*-inden-1-yl)carbamate: A mixture of tert-butyl (1*S*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-ylcarbamate (50 mg, 0.20 mmol), barium oxide (369 mg, 2.4 mmol), $\text{Ba}(\text{OH})_2$ (206 mg, 1.2 mmol) and CH_3I (28 mg, 0.20 mmol) in DMF (1.34 mL) was stirred at ambient temperature overnight. The reaction mixture was poured into saturated NaHCO_3 (15 mL), and the aqueous mixture was extracted with DCM (3 $\times$ 20 mL). The combined organic extracts were washed with water (3 $\times$ 15 mL), dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica gel chromatography (20 % EtOAc/hexanes) to yield the product as white waxy solid (17 mg, 32 % yield). ^1H NMR (CDCl_3) δ 7.18-7.30 (m, 4 H), 5.08 (m, 1 H), 4.72 (m, 1 H), 3.93-3.98 (m, 1 H), 3.50 (s, 3 H), 3.24-3.30 (m, 1 H), 2.83-2.88 (m, 1 H), 1.49 (s, 9 H) ppm.

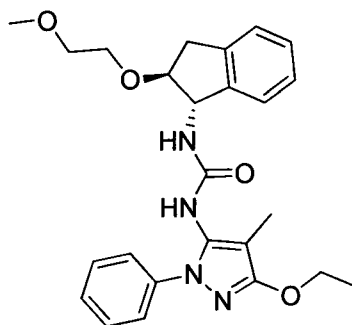
[00881] Step C: Preparation of 1-((1*S*,2*S*)-2-methoxy-2,3-dihydro-1*H*-inden-1-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)urea: A solution of tert-butyl (1*S*,2*S*)-2-methoxy-2,3-dihydro-1*H*-inden-1-ylcarbamate (15.9 mg, 0.0604 mmol) in hydrogen chloride (5-6 N in Isopropyl alcohol, 604 μL , 3.02 mmol) was stirred at ambient temperature for 1 hour. After removal of the solvent under vacuum, the white solid residue was taken up in DMA (302 μL), followed by addition of phenyl 2-phenyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-ylcarbamate (19.3 mg, 0.0604 mmol) and DIEA (52.6 μL , 0.302 mmol), and the reaction was stirred at ambient temperature for 20 minutes. The reaction mixture was directly purified by reverse-phase chromatography (5 to 60% acetonitrile/water) to yield the product as white solid (6 mg, 26% yield). MS (apci) m/z = 389.1 ($\text{M}+\text{H}$).

Example 48

1-((1S,2S)-2-(2-methoxyethoxy)-2,3-dihydro-1H-inden-1-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea

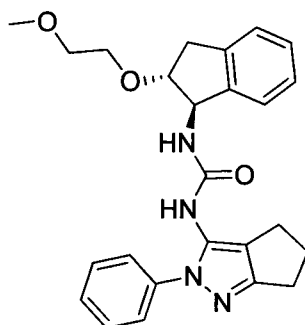
[00882] Step A: Preparation of tert-butyl ((1S,2S)-2-(2-methoxyethoxy)-2,3-dihydro-1H-inden-1-yl)carbamate: A mixture of tert-butyl (1S,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-ylcarbamate (50 mg, 0.20 mmol), barium oxide (369 mg, 2.4 mmol), Ba(OH)₂ (206 mg, 1.2 mmol) and 1-bromo-2-methoxyethane (28 mg, 0.20 mmol) in DMF (1.3 mL) was stirred at ambient temperature overnight. The reaction mixture was filtered (GF/F paper), rinsed with acetonitrile, concentrated and directly purified by reverse-phase chromatography (5 to 60% acetonitrile/water) to yield the product as white solid (14 mg, 23% yield). ¹H NMR (CDCl₃) δ 7.16-7.29 (m, 4 H), 5.08 (m, 1 H), 4.74-4.76 (m, 1 H), 4.08-4.12 (m, 1 H), 3.87-3.92 (m, 1 H), 3.73-3.79 (m, 1 H), 3.55-3.59 (m, 2 H), 3.38 (s, 3 H), 3.24-3.30 (m, 1 H), 2.90-2.95 (m, 1 H), 1.48 (s, 9 H)ppm.

[00883] Step B: Preparation of 1-((1S,2S)-2-(2-methoxyethoxy)-2,3-dihydro-1H-inden-1-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea: A solution of tert-butyl (1S,2S)-2-(2-methoxyethoxy)-2,3-dihydro-1H-inden-1-ylcarbamate (14 mg, 0.046 mmol) in hydrogen chloride (455 μL, 2.3 mmol) [5-6 N, IPA] was stirred at ambient temperature for 10 minutes, then concentrated under reduced pressure. The white solid residue was taken up in DMA (228 μL), followed by addition of phenyl 2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-ylcarbamate (15 mg, 0.046 mmol) and DIEA (40 μL, 0.23 mmol). The reaction was stirred at ambient temperature for 1 hour, and directly purified by reverse-phase chromatography (5 to 60% acetonitrile/water) to yield the product as white solid (15 mg, 76% yield). MS (apci) m/z = 433.2 (M+H).

Example 49

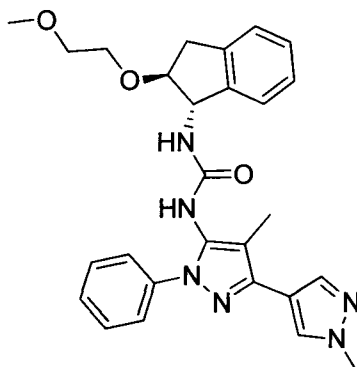
1-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((1S,2S)-2-(2-methoxyethoxy)-2,3-dihydro-1H-inden-1-yl)urea

[00884] To a turbid solution of (1S,2S)-2-(2-methoxyethoxy)-2,3-dihydro-1H-inden-1-amine hydrochloride (30 mg, 0.12 mmol) and phenyl 3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-ylcarbamate (39 mg, 0.12 mmol) in DMA (410 μ L) was added DIEA (107 μ L, 0.62 mmol) to obtain a clear solution, and the reaction was stirred at ambient temperature for 30 minutes. The reaction mixture was directly purified by reverse-phase chromatography (5 to 70% acetonitrile/water) to yield the product as white solid (27 mg, 49 % yield). MS (apci) m/z = 451.2 (M+H).

Example 50

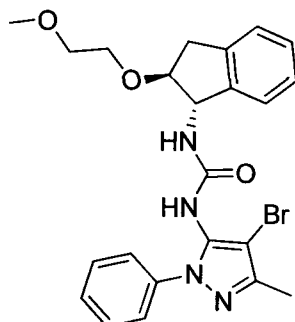
1-((1R,2R)-2-(2-methoxyethoxy)-2,3-dihydro-1H-inden-1-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea

[00885] The title product was prepared as described for Example 48, using (1R,2R)-1-amino-2,3-dihydro-1H-inden-2-ol instead of (1S,2S)-1-amino-2,3-dihydro-1H-inden-2-ol in the initial step. MS (apci) m/z = 433.2 (M+H).

Example 51

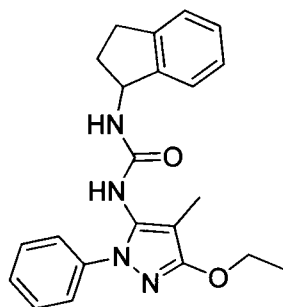
1-((1S,2S)-2-(2-methoxyethoxy)-2,3-dihydro-1H-inden-1-yl)urea-3-((1S,2S)-2-(2-methoxyethoxy)-2,3-dihydro-1H-inden-1-yl)urea

[00886] The title product was prepared as described for Example 48, using phenyl (1',4-dimethyl-1-phenyl-1*H*,1'*H*-[3,4'-bipyrazol]-5-yl)carbamate in the urea coupling step in place of phenyl 2-phenyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-ylcarbamate. MS (apci) *m/z* = 487.2 (M+H).

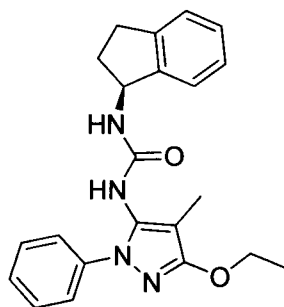
Example 52

1-((4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-3-((1S,2S)-2-(2-methoxyethoxy)-2,3-dihydro-1*H*-inden-1-yl)urea

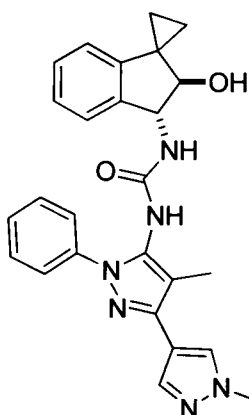
[00887] To a solution of phenyl 3-methyl-1-phenyl-1*H*-pyrazol-5-ylcarbamate (20 mg, 0.0682 mmol) in DCM (136 μ L) was added NBS (12.7 mg, 0.0716 mmol) in one portion, followed by pyridin-1-ium 4-methylbenzenesulfonate (PPTS, 1.71 mg, 0.00682 mmol). After stirring at ambient temperature for 10 minutes, (1*S*,2*S*)-2-(2-methoxyethoxy)-2,3-dihydro-1*H*-inden-1-amine hydrochloride (17.4 mg, 0.0716 mmol) was introduced, followed by DIEA (59.4 μ L, 0.341 mmol). The reaction was stirred for 1 hour and directly purified by reverse-phase chromatography (5 to 60% acetonitrile/water) to yield the product as white solid (17 mg, 50% yield). MS (apci) *m/z* = 485.0 (M+H).

Example 531-(2,3-dihydro-1H-inden-1-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea

[00888] The title product was as described for Example 49, using 2,3-dihydro-1H-inden-1-amine in place of (1*S*,2*S*)-2-(2-methoxyethoxy)-2,3-dihydro-1H-inden-1-amine hydrochloride. MS (apci) m/z = 376.9 (M+H).

Example 54(S)-1-(2,3-dihydro-1H-inden-1-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea

[00889] The title product was prepared as described for Example 53, using (*S*)-2,3-dihydro-1H-inden-1-amine instead of 2,3-dihydro-1H-inden-1-amine. MS (apci) m/z = 376.9 (M+H).

Example 55

1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(trans-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)urea

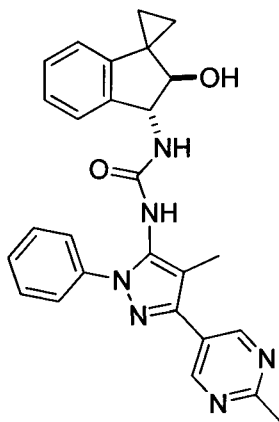
[00890] Step A: spiro[cyclopropane-1,1'-indene]: To a suspension of N-benzyl-N,N-diethylethanaminium chloride (111 mg, 0.487 mmol) in NaOH (50 wt % aqueous, 18 mL) cooled to 0 °C was added dropwise a solution of 1H-indene (4.463 g, 38.42 mmol) and

dibromoethane (6.6 mL, 76.84 mmol) in DMSO (7 mL). The reaction mixture was heated to 60 °C for 5 hours then cooled to ambient temperature. The reaction mixture was diluted with H₂O (30 mL) and extracted with Et₂O (3 x 30 mL). The combined organic phases were washed with H₂O (30 mL), then brine (3 x 30 mL), then dried (MgSO₄), filtered, and concentrated. The crude oil was purified by silica column chromatography eluting with hexanes to afford the title compound as a colorless oil (1.24 g, 23% yield). ¹H NMR (CDCl₃) δ 7.42 (m, 1H), 7.24 (m, 1H), 7.26 (m, 1H), 6.98 (m, 1H), 6.88 (d, 1H), 6.23 (d, 1H), 1.70-1.65 (m, 2H), 1.63-1.59 (m, 2H).

[00891] Step B: 1a',6a'-dihydrospiro[cyclopropane-1,6'-indeno[1,2-b]oxirene]: To a solution of spiro[cyclopropane-1,1'-indene] (817 mg, 5.745 mmol) in MeOH (40 mL) cooled to 0 °C were added DCC (2.37 g, 11.49 mmol), KHCO₃ (1.15 g, 11.49 mmol), then H₂O₂ (30% aqueous, 8 mL). The reaction mixture was allowed to warm to ambient temperature over 3 hours, then was diluted with saturated aqueous NaHCO₃ (50 mL) and H₂O (50 mL), and extracted with DCM (3 x 100 mL). The combined organic extracts were dried (MgSO₄), filtered, and concentrated to give the title compound as a colorless oil/white solid mixture, which was used in the next step without further purification.

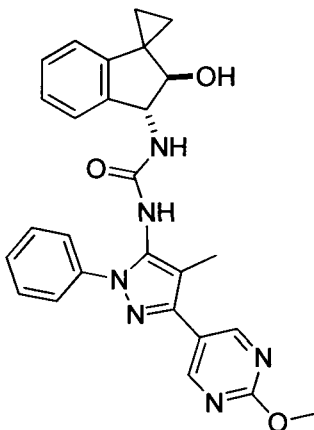
[00892] Step C: trans-3'-amino-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-ol: A mixture of 1a',6a'-dihydrospiro[cyclopropane-1,6'-indeno[1,2-b]oxirene] (909 mg, 5.75 mmol) and concentrated NH₄OH (22 mL) were heated to 60 °C for 1 hour. The reaction mixture was cooled, partially concentrated, then purified by reverse-phase column chromatography, eluting with 5-50% acetonitrile/water, to afford the title compound as a pale blue solid (493 mg, 49% yield). ¹H NMR (CDCl₃) δ 7.32 (m, 1H), 7.22 (m, 2H), 6.75 (m, 1H), 4.18 (d, 1H), 3.98 (d, 1H), 1.99 (br s, 3H), 1.35 (m, 1H), 1.12 (m, 1H), 0.97 (m, 1H), 0.69 (m, 1H).

[00893] Step D: 1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(trans-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)urea: To a solution of *trans*-3'-amino-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-ol (18.6 mg, 0.106 mmol) in *i*-PrOH (1 mL) was added phenyl (1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)carbamate (Intermediate 13, 41.6 mg, 0.111 mmol). The reaction mixture was heated to 75 °C for 1 hour, cooled to ambient temperature, then purified by reverse-phase column chromatography, eluting with 5-70% acetonitrile/water with 0.1% formic acid, to afford the title compound as a white solid (38.9 mg, 81% yield). MS (apci) *m/z* = 455.2 (M+H).

Example 56

1-(trans-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)-3-(4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-yl)urea

[00894] To a suspension of 4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-amine (Intermediate Y4, 22.7 mg, 0.086 mmol) in DCM (1 mL) were added triphosgene (12.7 mg, 0.043 mmol) then DIEA (0.045 mL, 0.257 mmol). The reaction mixture was stirred at ambient temperature for 2 hours, then a solution of *trans*-3'-amino-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-ol (Example 55, Step C, 15 mg, 0.086 mmol) and DIEA (0.045 mL, 0.257 mmol) in DCM (1 mL) was added. The reaction mixture was stirred at ambient temperature for 1 hour, concentrated, diluted with MeCN (1 mL) and stirred, and the resulting suspension was filtered and rinsed with Et₂O. The crude solid product was purified by silica column chromatography, eluting with 0-10% MeOH/DCM, to afford the title compound as a white solid (7.7 mg, 19% yield). MS (apci) *m/z* = 467.2 (M+H).

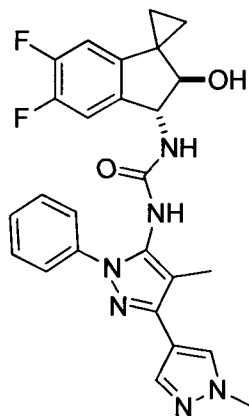
Example 57

1-(trans-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)-3-(3-(2-methoxypyrimidin-5-yl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea

[00895] Prepared according to the procedure for Example 56, replacing 4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-amine with 3-(2-methoxypyrimidin-5-yl)-4-

methyl-1-phenyl-1H-pyrazol-5-amine (Intermediate Y5, 24.1 mg, 0.086 mmol). The crude product was purified by preparatory TLC (1 mm plate), eluted with 10% MeOH/DCM, to afford the title compound as a white solid (10.4 mg, 25% yield). MS (apci) m/z = 483.2 (M+H).

Example 58



1-(trans-5',6'-difluoro-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)-3-(1',4'-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea

[00896] Step A: 5,6-difluoro-2,3-dihydro-1H-inden-1-ol: To a solution of 5,6-difluoro-2,3-dihydro-1H-inden-1-one (2.0 g, 11.90 mmol) in MeOH (40 mL) cooled to 0 °C was added NaBH₄ (540 mg, 14.27 mmol) in portions over 5 minutes. The reaction mixture was stirred at 0 °C for 1 hour, then allowed to warm to ambient temperature and stirred for 19 hours. The reaction mixture was diluted with H₂O (50 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO₄), filtered, and concentrated to afford the title compound as a colorless oil (2438 mg, 120% yield), which was used in the next step without purification and assuming theoretical yield. ¹H NMR (CDCl₃) δ 7.17 (dd, 1H), 7.00 (dd, 1H), 5.18 (t, 1H), 2.99 (m, 1H), 2.75 (m, 1H), 2.51 (m, 1H), 1.95 (m, 1H).

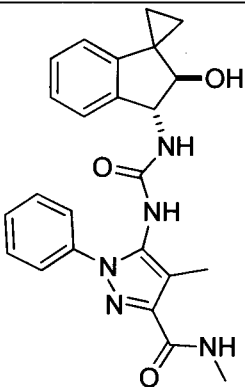
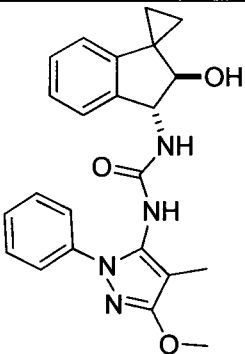
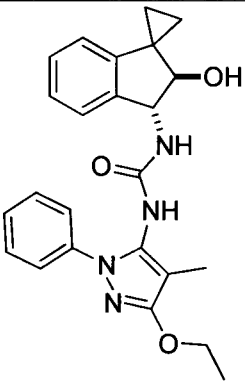
[00897] Step B: 5,6-difluoro-1H-indene: To a solution of 5,6-difluoro-2,3-dihydro-1H-inden-1-ol (2024 mg, 11.90 mmol) in toluene (40 mL) was added TsOH-H₂O (113 mg, 0.595 mmol). The reaction mixture heated to 110 °C for 1 hour, then cooled to ambient temperature. The reaction mixture was diluted with H₂O (50 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were dried (MgSO₄), filtered, and concentrated. The crude oil was purified by silica column chromatography eluting with hexanes to afford a colorless oil containing both the title compound and toluene (3.60 g, 200% yield). ¹H NMR (CDCl₃) δ 7.25 (m, 2H, toluene), 7.13-7.18 (m, 6H, product 2H and toluene 4H), 7.14 (m, 2H, product), 6.78 (m, 1H, product), 6.59 (m, 1H, product), 3.36 (m, 2H, product), 2.36 (s, 6H, toluene).

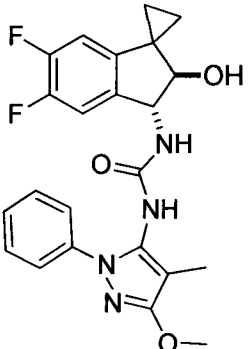
[00898] Step C: 1-(trans-5',6'-difluoro-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-

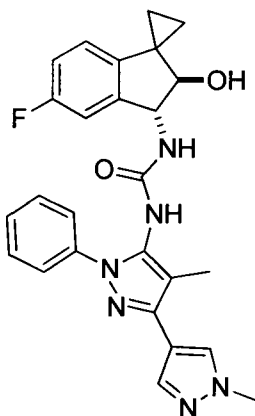
inden]-3'-yl)-3-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea: Prepared according to the procedure for Example 55, replacing 1H-indene in Step A with 5,6-difluoro-1H-indene, to afford the title compound as a white solid (13.9 mg, 86% yield). MS (apci) m/z = 491.2 (M+H).

[00899] The compounds of Table 2 were prepared according to the methods of Examples 55 and 58, replacing Intermediate 13 with the appropriate Intermediate 3, 5, or 11.

Table 2

Ex. #	Structure	name	MS (apci) m/z
59		215-(3-(<i>trans</i> -2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)ureido)-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide	432.2 (M+H)
60		1-(<i>trans</i> -2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)-3-(3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea	405.2 (M+H)
61		1-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-(<i>trans</i> -2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)urea	419.2 (M+H)

Ex. #	Structure	name	MS (apci) m/z
62		1-(<i>trans</i> -5',6'-difluoro-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)-3-(3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea	441.2 (M+H)

Example 63

1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(*trans*-5'-fluoro-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)urea

[00900] Step A: 5-fluoro-1H-indene: Prepared according to the procedure for Example 58, Steps A-B, replacing 5,6-difluoro-2,3-dihydro-1H-inden-1-one with 6-fluoro-2,3-dihydro-1H-inden-1-one to afford the title compound as a colorless oil (0.78 g, 87% yield). ¹H NMR (CDCl₃) δ 7.26 (dd, 1H), 7.07 (dd, 1H), 6.81-6.89 (m, 2H), 6.63 (m, 1H), 3.35 (m, 2H).

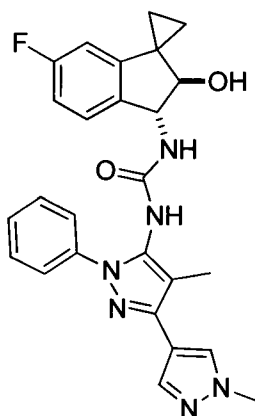
[00901] Step B: A 1:1 mixture of 5'-fluorospiro[cyclopropane-1,1'-indene] and 6'-fluorospiro[cyclopropane-1,1'-indene]: Prepared according to the procedure for Example 55, Step A, replacing 1H-indene with 5-fluoro-1H-indene to afford the title compound mixture as a colorless oil (183 mg, 20% yield). ¹H NMR (CDCl₃) δ 7.30 (dd, 1H), 7.09 (m, 1H), 6.92 (m, 1H), 6.81-6.86 (m, 4H), 6.66 (dd, 1H), 6.29 (d, 1H), 6.19 (d, 1H), 1.65-1.70 (m, 4H), 1.54-1.58 (m, 4H).

[00902] Step C: A 1:1 mixture of 1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(*trans*-5'-fluoro-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)urea and 1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(*trans*-6'-fluoro-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)urea: Prepared according to the procedure for

Example 55, Steps B-D, replacing spiro[cyclopropane-1,1'-indene] with a 1:1 mixture of 5'-fluorospiro[cyclopropane-1,1'-indene] and 6'-fluorospiro[cyclopropane-1,1'-indene] to afford the title compound mixture as a white solid (20.3 mg, 55% yield). MS (apci) $m/z = 473.2$ (M+H).

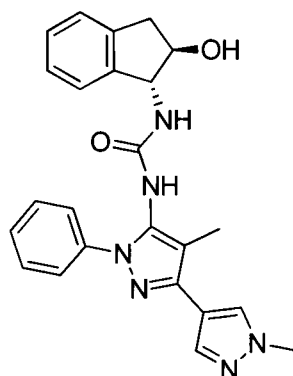
[00903] Step D: 1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(trans-5'-fluoro-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)urea: A 1:1 mixture of 1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(trans-5'-fluoro-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)urea and 1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(trans-6'-fluoro-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)urea (20.3 mg, 0.043 mmol) was purified by chiral HPLC on a Chiral Tech IA column (4.6 mm x 250 mm, 5 μ), eluted with 25% EtOH/hexanes, and the second of the two product peaks to elute was collected to afford the title compound as a white solid (4.5 mg, 22% yield). MS (apci) $m/z = 473.2$ (M+H). ^1H NMR (CD_2Cl_2) δ 7.80 (d, 1H), 7.45-7.53 (m, 5H), 7.38 (m, 1H), 6.88 (dt, 1H), 6.74 (d, 1H), 6.67 (dd, 1H), 4.96 (d, 1H), 3.99 (d, 1H), 3.91 (s, 3H), 2.14 (s, 3H), 1.31 (m, 1H), 1.00 (m, 1H), 0.85 (m, 1H), 0.59 (m, 1H).

Example 64



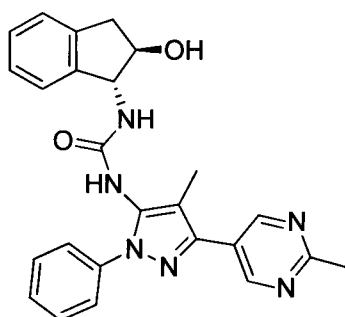
1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(trans-6'-fluoro-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)urea

[00904] Prepared according to the procedure for Example 63, but in Step D the first of the two product peaks to elute was collected to afford the title compound as a white solid (3.7 mg, 18% yield). MS (apci) $m/z = 473.2$ (M+H). ^1H NMR (CD_2Cl_2) δ 7.80 (d, 1H), 7.45-7.53 (m, 5H), 7.38 (m, 1H), 6.99 (m, 1H), 6.81 (dt, 1H), 6.41 (dd, 1H), 4.92 (d, 1H), 3.97 (d, 1H), 3.91 (s, 3H), 2.14 (s, 3H), 1.37 (m, 1H), 1.00 (m, 1H), 0.91 (m, 1H), 0.66 (m, 1H).

Example 65

1-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-3-(4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-yl)urea

[00905] To a turbid solution of (1R,2R)-1-amino-2,3-dihydro-1H-inden-2-ol (50 mg, 0.335 mmol) in iPrOH (1.4 mL) was added phenyl (1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrzazol]-5-yl)carbamate (125 mg, 0.335 mmol) in one portion. The white suspension was stirred in a 40 °C sand bath for 2 hours, then heated to reflux. It was then slowly cooled to ambient temperature and filtered, rinsed with IPA, MeOH and ether (10 mL each), yielding the title product as fine white solid (90 mg, 63% yield). ¹H NMR (400 MHz, *d*⁶-DMSO) δ 8.06 (s, 1H), 7.94 (br s, 1H), 7.74 (s, 1H), 7.56-7.58 (m, 2H), 7.45-7.50 (m, 2H), 7.34-7.38 (m, 1 H), 7.12-7.17 (m, 3H), 6.91-6.93 (m, 1H), 6.78 (d, *J*=8.6 Hz, 1H), 5.25 (br d, *J*=5.5 Hz, 1H), 4.83 (br t, *J*=7.4 Hz, 1H), 4.13-4.18 (m, 1H), 3.88 (s, 3H), 3.03-3.08 (m, 1H), 2.61-2.67 (m, 1H), 2.05 (s, 3H). MS (apci) *m/z* = 429.2 (M+H).

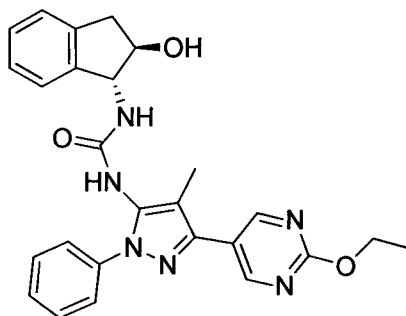
Example 66

1-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-3-(4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-yl)urea

[00906] To an orange suspension of 4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-amine (Intermediate Y4, 53.4 mg, 0.20 mmol) in DriSolve DCM (1.0 mL) was added triphosgene (29.8 mg, 0.10 mmol), followed by DIEA (105 μL, 0.60 mmol). After 2 hours, (1R,2R)-1-amino-2,3-dihydro-1H-inden-2-ol (30 mg, 0.20 mmol) was added in one portion. After 30 minutes, the reaction mixture was vacuum-filtered, rinsed with DCM and ether (2 mL

each), giving the product as white powder (54 mg, 58% yield). ^1H NMR (400 MHz, d^6 -DMSO) δ 9.01 (s, 2H), 8.40 (br s, 1H), 7.62-7.64 (m, 2H), 7.49-7.54 (m, 2H), 7.40-7.44 (m, 1 H), 7.11-7.19 (m, 3H), 6.87-6.91 (m, 2H), 5.26 (br d, $J=5.5$ Hz, 1H), 4.83 (br t, $J=7.8$ Hz, 1H), 4.12-4.19 (m, 1H), 3.03-3.09 (m, 1H), 2.66 (s, 3H), 2.61-2.66 (m, 1H), 2.15 (s, 3H). MS (apci) m/z = 441.2 (M+H).

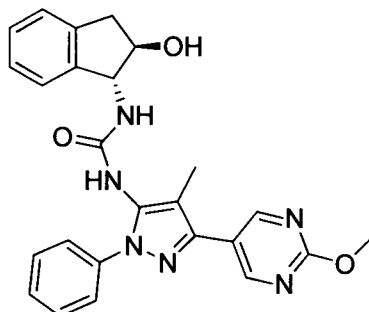
Example 67



1-(3-(2-ethoxypyrimidin-5-yl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)urea

[00907] The title product was prepared as described for Example 66, using 3-(2-ethoxypyrimidin-5-yl)-4-methyl-1-phenyl-1H-pyrazol-5-amine (49.5 mg, 0.17 mmol) instead of 4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-amine. The product was isolated as white solid (51 mg, 61% yield). ^1H NMR (400 MHz, d^6 -DMSO) δ 8.90 (s, 2H), 7.61-7.63 (m, 2H), 7.48-7.53 (m, 2H), 7.40-7.43 (m, 1 H), 7.25-7.31 (m, 1H), 7.14 (m, 3H), 6.84-6.91 (m, 2H), 5.26 (br d, $J=5.5$ Hz, 1H), 4.83 (br t, $J=7.8$ Hz, 1H), 4.39 (q, $J=7.0$ Hz, 2H), 4.11-4.19 (m, 1H), 3.03-3.08 (m, 1H), 2.61-2.67 (m, 1H), 2.12 (s, 3H), 1.35 (t, $J=7.0$ Hz, 3H). MS (apci) m/z = 471.2 (M+H).

Example 68

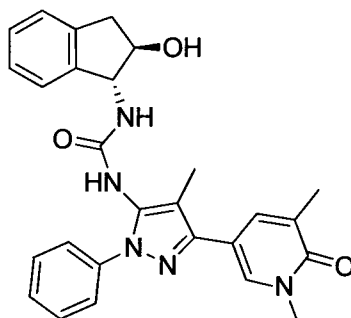


1-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-3-(3-(2-methoxypyrimidin-5-yl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea

[00908] The title product was prepared as described for Example 66, using 3-(2-methoxypyrimidin-5-yl)-4-methyl-1-phenyl-1H-pyrazol-5-amine (47 mg, 0.17 mmol) instead of 4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-amine. The product was isolated

as white solid (50 mg, 62% yield). ^1H NMR (400 MHz, d^6 -DMSO) δ 8.92 (s, 2H), 7.61-7.63 (m, 2H), 7.49-7.53 (m, 2H), 7.40-7.43 (m, 1H), 7.24-7.30 (m, 1H), 7.11-7.17 (m, 3H), 6.85-6.92 (m, 2H), 5.26 (br d, $J=5.5$ Hz, 1H), 4.83 (br t, $J=7.4$ Hz, 1H), 4.12-4.18 (m, 1H), 3.96 (s, 3H), 3.03-3.09 (m, 1H), 2.61-2.67 (m, 1H), 2.12 (s, 3H). MS (apci) m/z = 457.2 (M+H).

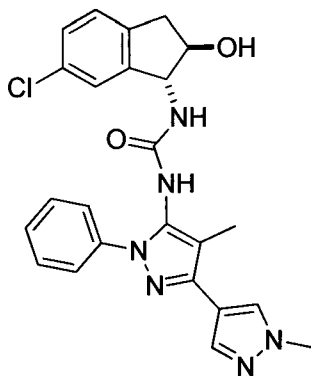
Example 69



1-(3-(1,5-dimethyl-6-oxo-1,6-dihydropyridin-3-yl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)urea

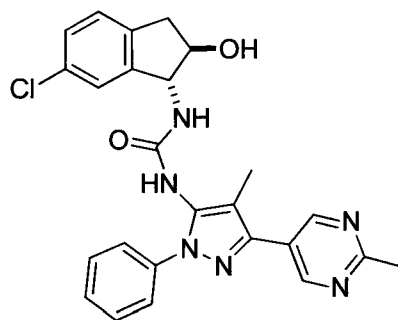
[00909] The title product was prepared as described for Example 66, using 5-(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)-1,3-dimethylpyridin-2(1H)-one (49 mg, 0.17 mmol) instead of 4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-amine. The product was isolated as white solid (45 mg, 54% yield). MS (apci) m/z = 468.2 (M-H).

Example 70



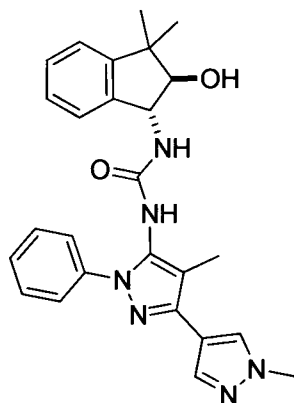
1-((1,2-*trans*)-6-chloro-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-3-(1',4'-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea

[00910] The title product was prepared as described for Example 65, using *trans*-1-amino-6-chloro-2,3-dihydro-1H-inden-2-ol (30 mg, 0.16 mmol) instead of (1R,2R)-1-amino-2,3-dihydro-1H-inden-2-ol. The product was isolated as crystalline white solid (65 mg, 84% yield). ^1H NMR (400 MHz, d^6 -DMSO) δ 8.03 (s, 1H), 7.99 (br s, 1H), 7.73 (s, 1H), 7.55-7.58 (m, 2H), 7.45-7.49 (m, 2H), 7.33-7.37 (m, 1H), 7.15-7.22 (m, 2H), 6.93 (br, 1H), 6.90 (m, 1H), 5.33 (br d, $J=5.9$ Hz, 1H), 4.81 (br t, $J=7.8$ Hz, 1H), 4.14-4.21 (m, 1H), 3.87 (s, 3H), 3.00-3.06 (m, 1H), 2.57-2.63 (m, 1H), 2.04 (s, 3H). MS (apci) m/z = 461.1 (M-H).

Example 71

1-((1,2-*trans*)-6-chloro-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-3-(4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-yl)urea

[00911] The title product was prepared as described for Example 66, using *trans*-1-amino-6-chloro-2,3-dihydro-1H-inden-2-ol (30 mg, 0.16 mmol) instead of (1R,2R)-1-amino-2,3-dihydro-1H-inden-2-ol. The product was isolated as crystalline white solid (12 mg, 44% yield). MS (apci) m/z = 473.2 (M-H).

Example 72

1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-((1,2-*trans*)-2-hydroxy-3,3-dimethyl-2,3-dihydro-1H-inden-1-yl)urea

[00912] Step 1. Synthesis of 3,3-dimethyl-2,3-dihydro-1H-inden-1-ol. A light suspension of 3,3-dimethyl-2,3-dihydro-1H-inden-1-one (2.5 g, 16 mmol) in DriSolve MeOH (52 mL) was first cooled in an ice-water bath, followed by addition of NaBH₄ (0.71 g, 19 mmol) in small portions. The reaction was then warmed up to ambient temperature and stirred for 30 minutes. The reaction was poured onto ice water (50 mL) in a separatory funnel, rinsed over with water, giving a white suspension. The suspension was extracted with DCM (3 × 50 mL). The combined organic extracts were washed with water, brine (50 mL each), dried (Na₂SO₄), filtered and concentrated to yield the crude product as clear colorless oil (2.5 g, 99% yield), which was used for the next reaction without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.40 (m, 1H), 7.17-7.31 (m, 3H), 5.23-5.28 (m, 1H), 2.35-2.40 (m, 1H), 1.79-1.85 (m, 2H),

1.39 (s, 3H), 1.22 (s, 3H).

[00913] Step 2. Synthesis of 1,1-dimethyl-1H-indene. A clear colorless solution of 3,3-dimethyl-2,3-dihydro-1H-inden-1-ol (1.83 g, 11.3 mmol) and 4-methylbenzenesulfonic acid hydrate (0.107 g, 0.564 mmol) [5 mol%] in toluene (37.6 mL) was stirred at 110 °C for 2 hours. The light yellowish reaction solution was cooled to ambient temperature, diluted with Et₂O (50 mL) and washed with saturated aqueous NaHCO₃ and brine (50 mL each). The organic layer was phase-separated and dried over Na₂SO₄, then concentrated in vacuo. The crude was taken up in hexanes and purified by silica chromatography (hexanes) to yield the product as clear colorless oil (0.85 g, 52% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.28-7.32 (m, 2H), 7.16-7.23 (m, 2H), 6.62 (d, *J*=6.3 Hz 1H), 6.36 (d, *J*=5.5 Hz, 1H), 1.31 (s, 6H).

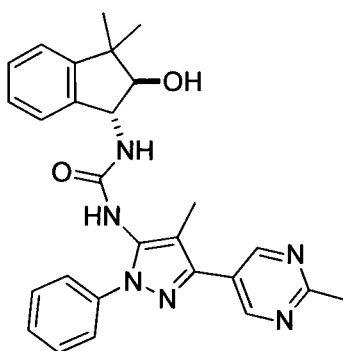
[00914] Step 3. Synthesis of 6,6-dimethyl-6,6a-dihydro-1aH-indeno[1,2-b]oxirene. To a solution of 1,1-dimethyl-1H-indene (590 mg, 4.09 mmol) in DCM (20 mL) was added mCPBA (1210 mg, 4.91 mmol) in four portions at 20-minute intervals and stirred at ambient temperature for 5 hours. The reaction was treated with saturated aqueous NaHCO₃ (20 mL), stirred for an additional 30 minutes, and then diluted with water and DCM (20 mL each). The aqueous layer was separated and extracted with DCM (2 × 30 mL). The combined organic layers was dried (Na₂SO₄), filtered and concentrated. The crude product was purified by silica chromatography (DCM) to yield the product. ¹H NMR (400 MHz, CDCl₃) δ 7.23-7.31 (m, 2H), 7.15-7.20 (m, 2H), 4.24 (d, *J*=2.7 Hz 1H), 3.71 (d, *J*=2.7 Hz, 1H), 1.41 (s, 3H), 1.23 (s, 3H).

[00915] Step 4. Synthesis of (2,3-*trans*)-3-amino-1,1-dimethyl-2,3-dihydro-1H-inden-2-ol. A mixture of 6,6-dimethyl-6,6a-dihydro-1aH-indeno[1,2-b]oxirene (0.35 g, 2.2 mmol) in concentrated NH₄OH (3.8 g, 109 mmol) was stirred at 60 °C for 6 hours. The reaction mixture was briefly subjected to mild vacuum, then filtered and rinsed with water. The solid was then rinsed with small amount of ether to yield first batch of product as fine solid (13 mg). To recover additional product, the aqueous layer and ether filtrate were concentrated and treated with reverse-phase chromatography (C18, 5 to 40% acetonitrile/water) to yield a second batch of product as solid (78 mg). ¹H NMR (400 MHz, CDCl₃) δ 7.22-7.29 (m, 3H), 7.15-7.18 (m, 1H), 4.08 (d, *J*=8.2 Hz 1H), 3.65 (d, *J*=8.2 Hz, 1H), 2.79 (br, 3H), 1.36 (s, 3H), 1.11 (s, 3H).

[00916] Step 5. Synthesis of 1-(1',4'-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-((1,2-*trans*)-2-hydroxy-3,3-dimethyl-2,3-dihydro-1H-inden-1-yl)urea. To a clear solution of (2,3-*trans*)-3-amino-1,1-dimethyl-2,3-dihydro-1H-inden-2-ol (12 mg, 0.0677 mmol) in iPrOH (282 μL) was added phenyl (1',4'-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)carbamate (25.3 mg, 0.0677 mmol) in one portion. The resulting milky suspension was stirred at 40 °C for 4 hours and then brought to reflux. The reaction mixture was slowly cooled to ambient

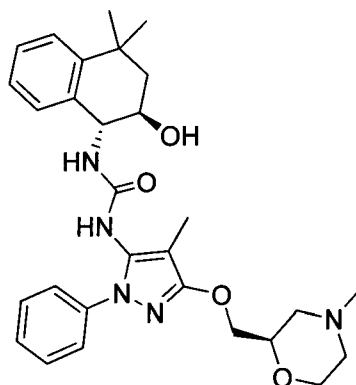
temperature and stirred for another 1 hour. The reaction mixture was vacuum-filtered, rinsed with iPrOH and ether (2 mL each), giving first batch product (14 mg). A second batch of product was obtained from reverse-phase purification of the filtrate (C18, 5 to 60% acetonitrile/water). The two batch of product was combined to give a white solid (26 mg, 82% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.84 (s, 1H), 7.76 (s, 1H), 7.56-7.60 (m, 2H), 7.45-7.50 (m, 2H), 7.35-7.39 (m, 1H), 7.25-7.29 (m, 1H), 7.16-7.20 (m, 3H), 6.94-6.96 (m, 1H), 5.55 (br, 1H), 5.04 (m, 1H), 3.94 (s, 3H), 3.66 (d, *J*=8.2 Hz, 1H), 2.29 (s, 3H), 1.34 (s, 3H), 1.10 (s, 3H). MS (apci) *m/z* = 457.2 (M+H).

Example 73



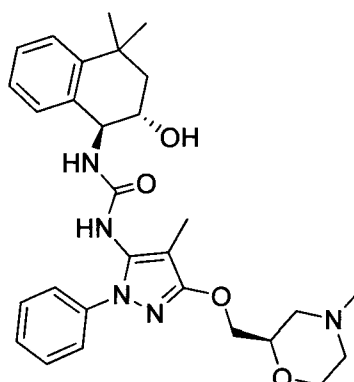
1-((1,2-*trans*)-2-hydroxy-3,3-dimethyl-2,3-dihydro-1H-inden-1-yl)-3-(4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-yl)urea

[00917] To a suspension of 4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-amine (Intermediate Y4, 37 mg, 0.14 mmol) in DriSolve DCM (0.7 mL) was added triphosgene (21 mg, 0.07 mmol), followed by DIEA (74 μL, 0.4 mmol). After 1 hour, *trans*-3-amino-1,1-dimethyl-2,3-dihydro-1H-inden-2-ol (25 mg, 0.14105 mmol) was added in one portion. After 30 minutes, the reaction was concentrated and directly purified by reverse-phase chromatography (C18, 5 to 60% acetonitrile/water with 0.1 v/v% formic acid) to yield the product as white solid (20 mg, 29% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.97 (s, 2H), 7.57-7.59 (m, 2H), 7.43-7.47 (m, 2H), 7.34-7.38 (m, 1H), 7.25-7.30 (m, 2H), 7.14-7.18 (m, 2H), 6.94-6.96 (m, 1H), 5.48 (br, 1H), 5.00 (br t, *J*=7.0 Hz, 1H), 3.72 (d, *J*=7.8 Hz, 1H), 2.76 (s, 3H), 2.21 (s, 3H), 1.33 (s, 3H), 1.20 (m, 1H), 1.08 (s, 3H). MS (apci) *m/z* = 467.2 (M-H).

Example 74

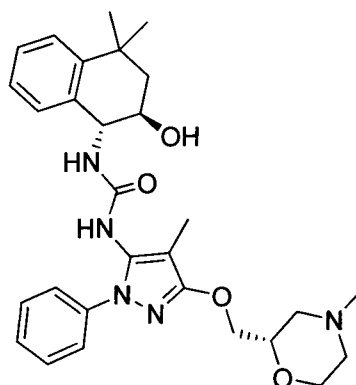
1-(((1R, 2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-(((R)-4-methylmorpholin-2-yl)methoxy)-1-phenyl-1H-pyrazol-5-yl)urea

[00918] To a solution of triphosgene (44.1 mg, 0.146 mmol) in dry CH₂Cl₂ (1.0 mL) was added a solution of (R)-4-methyl-3-((4-methylmorpholin-2-yl)methoxy)-1-phenyl-1H-pyrazol-5-amine (Intermediate Y2, 110 mg, 0.364 mmol) and DIEA (76.0 μL, 0.437 mmol) in dry CH₂Cl₂ (1.0 mL) dropwise over 45 minutes. The mixture was stirred for 15 minutes and (1R,2R)-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Intermediate X2, 83.5 mg, 0.437 mmol) was added. The reaction mixture was stirred for 16 hours and was diluted with CH₂Cl₂ (4 mL). The mixture was washed with 1M NaOH (2X) and H₂O. The organic portion was dried over Na₂SO₄, filtered, concentrated and the residue purified on a SiO₂ column (EtOAc, 5%, 10% MeOH/EtOAc). The resulting white foam was dissolved in 50% CH₂Cl₂-hexanes and concentrated to provide the title compound as a white solid that was dried in vacuum (187 mg, 99%). MS(apci) m/z = 520.3 (M+H).

Example 75

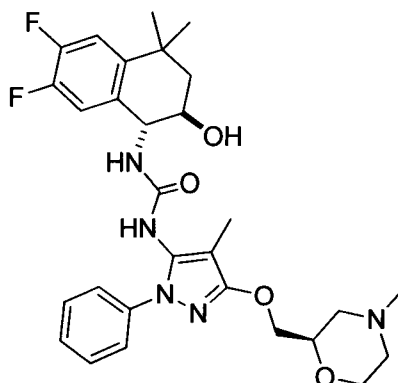
1-(((1S, 2S)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-(((R)-4-methylmorpholin-2-yl)methoxy)-1-phenyl-1H-pyrazol-5-yl)urea

[00919] Using (1S,2S)-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Intermediate X3) in the procedure for Example 74, the title compound was obtained as a white solid (94 mg, 55%). MS(apci) m/z = 520.3 (M+H).

Example 76

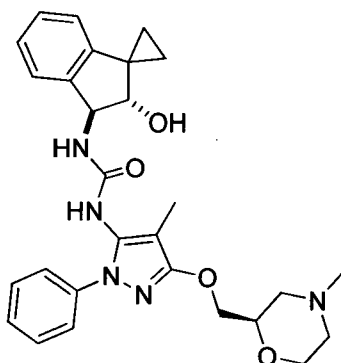
1-((1R, 2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-(((S)-4-methylmorpholin-2-yl)methoxy)-1-phenyl-1H-pyrazol-5-yl)urea

[00920] Using (S)-4-methyl-3-((4-methylmorpholin-2-yl)methoxy)-1-phenyl-1H-pyrazol-5-amine (Intermediate Y1) in the procedure for Example 74, the title compound was obtained as a white solid (54 mg, 35%). MS(apci) m/z = 520.3 (M+H).

Example 77

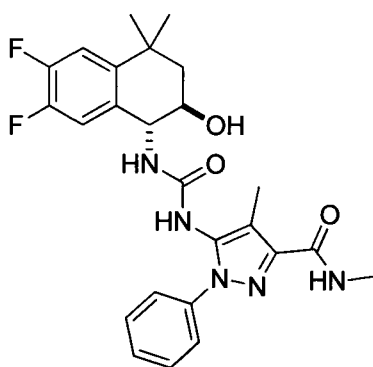
1-(trans-6,7-difluoro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-(((R)-4-methylmorpholin-2-yl)methoxy)-1-phenyl-1H-pyrazol-5-yl)urea

[00921] Using *trans*-1-amino-6,7-difluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol in the procedure described for Example 74, the title compound was obtained as a white solid (31 mg, 28%). MS(apci) m/z = 556.3 (M+H).

Example 78

1-((trans-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)-3-(4-methyl-3-(((R)-4-methylmorpholin-2-yl)methoxy))-1-phenyl-1H-pyrazol-5-yl)urea

[00922] To a solution of (R)-4-methyl-3-((4-methylmorpholin-2-yl)methoxy)-1-phenyl-1H-pyrazol-5-amine (Intermediate Y2, 51.8 mg, 0.171 mmol) in dry DMF (1.0 mL) was added carbonyldiimidazole (33.3 mg, 0.205 mmol) and the mixture was stirred at ambient temperature for 64 hours. The reaction mixture was treated with *trans*-3'-amino-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-ol (Example 55, Step C, 30.0 mg, 0.171 mmol) in dry DMF (0.5 mL) and stirred for 8 hours. The reaction mixture was added to H₂O (6 mL), treated with 2M NaOH to pH=11 and extracted with EtOAc (4X). The combined extracts were washed with saturated NaCl (2X), dried over MgSO₄/activated charcoal, filtered and concentrated. The residue was purified on a SiO₂ column (EtOAc, 5%, 10% (9:1 MeOH/NH₄OH)/EtOAc) to provide the title compound as a white solid (36 mg, 42%). MS(apci) m/z = 504.2 (M+H).

Example 79

5-(3-(((1,2-trans)-6,7-difluoro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ureido)-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide

[00923] Step A: Preparation of 6,7-difluoro-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one: A stainless steel bomb equipped with a Teflon insert and a stir bar was charged with 1,2-difluorobenzene (9.5 g, 83 mmol), 5,5-dimethyldihydrofuran-2(3H)-one (9.5 g, 83 mmol), and lastly aluminum trichloride (13 g, 100 mmol). The reaction mixture was heated to 100 °C overnight with stirring behind a safety shield. The reaction mixture was cooled to ambient

temperature and the bomb was placed in an ice bath before opening. The reaction mixture was partitioned between water (100 mL) and EtOAc (150 mL). The phases were separated and the aqueous phase was extracted aqueous with EtOAc (2 x 50 mL). The combined organic phases were washed with saturated NaHCO₃ (100 mL), dried (MgSO₄), filtered, and concentrated. The crude material was purified by Redi-Sep 330 silica gel column, eluting with 10% EtOAc/hexanes. Yield: 4.4 g (24%).

[00924] Step B: Preparation of 6,7-difluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol: A round bottomed flask was charged with 6,7-difluoro-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (4.4 g, 21 mmol) and MeOH (75 mL). Next added NaBH₄ (0.87 g, 23 mmol) in portions over a 15 minute period. The reaction mixture was stirred at ambient temperature for 3 hours and then concentrated under vacuum. The residue was partitioned between 2N NaOH (30 mL) and EtOAc (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (50 mL). The combined organic phases were washed with brine (30 mL), dried (MgSO₄), filtered, and concentrated. Yield: 4.6 g (93%).

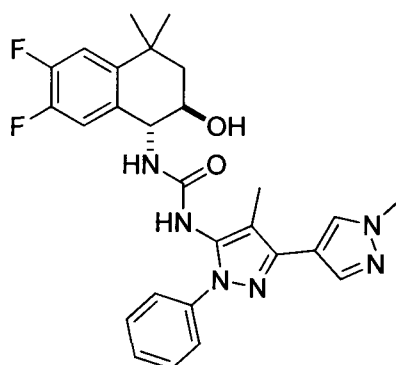
[00925] Step C: Preparation of 6,7-difluoro-1,1-dimethyl-1,2-dihydronaphthalene: A round bottomed flask was charged with 6,7-difluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (4.4 g, 21 mmol), 1,2-dichloroethane (50 mL) and 4-methylbenzenesulfonic acid hydrate (0.20 g, 1.0 mmol). The reaction mixture was heated to 60 °C for 1 hour. The reaction mixture was allowed to cool to ambient temperature. The crude reaction mixture was used directly into the next step without workup.

[00926] Step D: Preparation of 5,6-difluoro-3,3-dimethyl-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene: The reaction mixture from Step C was cooled in an ice bath and saturated aqueous NaHCO₃ (50 mL) was added. 3-chlorobenzoperoxoic acid (5.6 g, 23 mmol) was added in portions over a 10 min period, and the reaction mixture was allowed to warm to ambient temperature and was stirred vigorously overnight. The reaction mixture was filtered through GF/F paper, rinsing with DCM. The phases were separated and the aqueous phase was extracted with DCM (50 mL). The combined organic phases were washed with 1N NaOH (50 mL). The resulting emulsion was filtered through GF/F paper which allowed the phases to separate. The organic phase was dried over Na₂SO₄, filtered, and concentrated in vacuo (rotary evaporator, water temperature was set to 30 °C to avoid loss of product). The crude material was placed under high vacuum for 10 minutes to provide 5.7 g of crude product, which was used the next step without purification.

[00927] Step E: Preparation of *trans*-1-amino-6,7-difluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol: A stainless steel bomb equipped with a Teflon insert and a stir bar

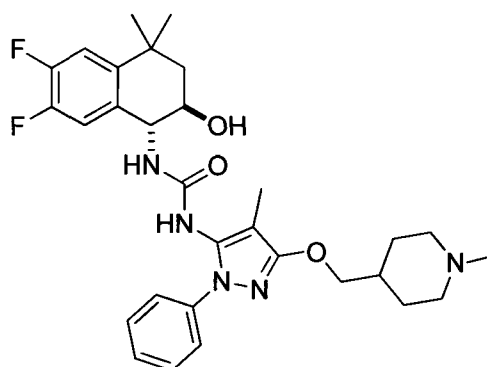
was charged with 5,6-difluoro-3,3-dimethyl-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene (4.3 g, 20 mmol), using a few mL's of EtOH to transfer, followed by addition aqueous ammonium hydroxide (30 mL). The reaction mixture was heated to 90 °C in an oil bath overnight with stirring. The reaction mixture was cooled to ambient temperature and the bomb was placed in an ice bath before opening. The contents of the bomb were transferred to a round bottomed flask (using EtOH to rinse the bomb) and concentrated in vacuo. EtOH (3 x 30 mL) was used to azeotrope residual water and ammonium hydroxide. The residue was partitioned between 2N aqueous HCl (75 mL) and diethyl ether (75 mL). The phases were separated and the organic phase was extracted with 1N HCl (25 mL). The combined organic phases were extracted with diethyl ether (50 mL). The aqueous phase was chilled in an ice bath and basified with NaOH pellets (added 5-6 at a time with some sonication to dissolve, until pH was >12). The product precipitated out of the basic aqueous phase. The product was extracted with 2:1 diethyl ether/EtOAc (3 x 50 mL). The combined organic phases were dried (Na₂SO₄), filtered, and concentrated to give the desired product. Yield: 1.7 g (33%).

[00928] Step F: Preparation of 5-(3-((1,2-*trans*)-6,7-difluoro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ureido)-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide: A vial was charged with 5-amino-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide (Intermediate 10; 25 mg, 0.11 mmol), DCM (0.5 mL) and N-ethyl-N-isopropylpropan-2-amine (58 µL, 0.33 mmol). Triphosgene (20 mg, 0.066 mmol) was added, and the reaction mixture was stirred for 15 minutes. *trans*-1-amino-6,7-difluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (25 mg, 0.11 mmol) was added, followed by N-ethyl-N-isopropylpropan-2-amine (58 µL, 0.33 mmol). The reaction mixture was stirred over the weekend for convenience. The reaction mixture was diluted with water and DCM. The phases were separated and the aqueous phase was extracted with DCM. The combined organic phases were dried (MgSO₄), filtered, and concentrated. The crude material was purified by preparative HPLC using reverse phase YMC ODS-AQ (250 x 20 mm) column. Fractions containing the product were pooled and concentrated, and then partitioned between EtOAc (10 mL) and saturated NaHCO₃ (10 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried (MgSO₄), filtered, and concentrated. The product was further purified by preparative TLC (0.5 mm thickness, R_f = 0.60) eluting with 10% MeOH/DCM. Yield: 9 mg (17%). MS m/z (APCI-neg) M-1 = 482.2.

Example 80

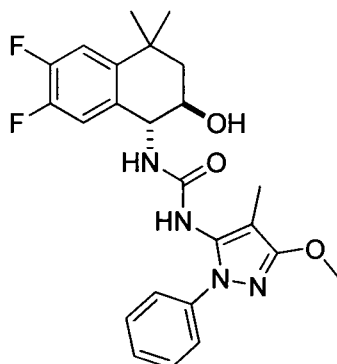
1-((1,2-*trans*)-6,7-difluoro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(1',4'-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea

[00929] The title compound was prepared from (1,2-*trans*)-1-amino-6,7-difluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Example 79, Step E; 25 mg, 0.11 mmol) and 1',4'-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-amine (Intermediate 12, Step C; 28 mg, 0.11 mmol) according to the procedure described for Example 79, Step F. Yield: 9 mg (16%). MS m/z (APCI-pos) $M+1 = 507.2$.

Example 81

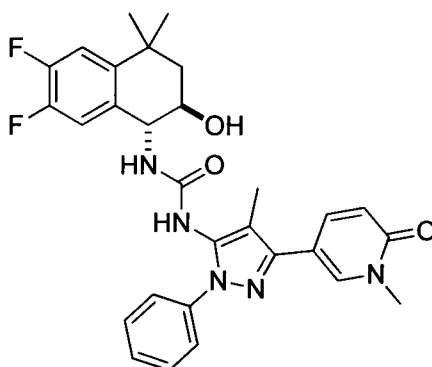
1-((1,2-*trans*)-6,7-difluoro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-((1-methylpiperidin-4-yl)methoxy)-1-phenyl-1H-pyrazol-5-yl)urea

[00930] The title compound was prepared from (1,2-*trans*)-1-amino-6,7-difluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Example 79, Step E; 25 mg, 0.11 mmol) and 4-methyl-3-((1-methylpiperidin-4-yl)methoxy)-1-phenyl-1H-pyrazol-5-amine (Intermediate Y3; 33 mg, 0.11 mmol) according to the procedure described for Example 79, Step F. Yield: 10 mg (16%). MS m/z (APCI-pos) $M+1 = 554.3$.

Example 82

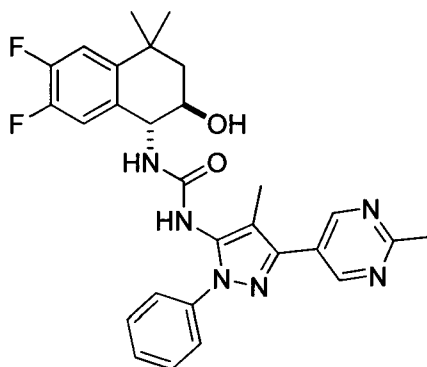
1-((1,2-*trans*)-6,7-difluoro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea

[00931] The title compound was prepared from *trans*-1-amino-6,7-difluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Example 79, Step E; 25 mg, 0.11 mmol) and 3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-amine (Intermediate 2; 22 mg, 0.11 mmol) according to the procedure described for Example 79, Step F. Yield: 6 mg (12%). MS *m/z* (APCI-neg) *M*-1 = 455.1.

Example 83

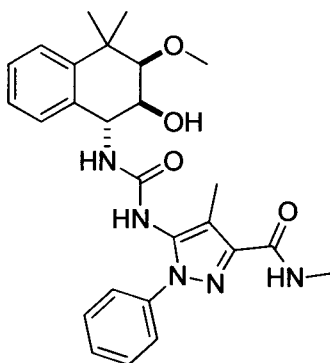
1-((1,2-*trans*)-6,7-difluoro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)urea

[00932] The title compound was prepared from *trans*-1-amino-6,7-difluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Example 79, Step E; 25 mg, 0.11 mmol) and 5-(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)-1-methylpyridin-2(1H)-one (Intermediate 7; 31 mg, 0.11 mmol) according to the procedure described for Example 79, Step F. Yield: 2 mg (3%). MS *m/z* (APCI-neg) *M*-1 = 532.2.

Example 84

1-((1,2-*trans*)-6,7-difluoro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-yl)urea

[00933] The title compound was prepared from *trans*-1-amino-6,7-difluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Example 79, Step E; 25 mg, 0.11 mmol) and 4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-amine (Intermediate Y4, 29 mg, 0.11 mmol) according to the procedure described for Example 79, Step F. Yield: 8 mg (14%). MS *m/z* (APCI-neg) *M*-1 = 517.2.

Example 85

5-(3-((*r*-1,*t*-2,*t*-3)-2-hydroxy-3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ureido)-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide

[00934] Step A: Preparation of 1-methylnaphthalen-2-ol: A round bottomed flask was charged with naphthalen-2-ol (100 g, 694 mmol) and anhydrous MeOH (250 mL). The solution was chilled in an ice bath and sodium methanolate (158 mL, 694 mmol; 25 wt% in MeOH) was added by addition funnel over 1 hour under a stream of N₂ with stirring. The ice bath was removed and the reaction mixture was stirred for 30 minutes at ambient temperature. The reaction mixture was concentrated mixture in vacuo, using toluene (3 x 150 mL) to azeotrope residual MeOH. The resulting solids were dried under high vacuum. The solids were suspended in anhydrous toluene (500 mL), and iodomethane (129 mL, 2076 mmol) was added while stirring. The mixture was heated to reflux (oil bath temp = 70 °C) under N₂ overnight. Due to

incomplete reaction, additional iodomethane (100 mL) was added, and the reaction mixture was heated at 70-75 °C for 2 days. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. The residue was partitioned between 1N NaOH (600 mL) and diethyl ether (400 mL). The phases were separated and the organic phase was extracted with 1N NaOH (200 mL). The combined aqueous phases were extracted with diethyl ether (300 mL). The aqueous phases was then chilled in an ice bath, and carefully acidified with concentrated HCl (approximately 70 mL), and then extracted with diethyl ether (3 x 100 mL). The combined organic phases were dried (MgSO₄), filtered, and concentrated, then dried under high vacuum for one hour to provide 57.8 g of brown solids containing a 69:31 ratio of desired 1-methylnaphthalen-2-ol to starting material naphthalen-2-ol was obtained. The mixture was carried forward to the next step without separation.

[00935] Step B: Preparation of 1,1-dimethylnaphthalen-2(1H)-one: A round bottomed flask was charged with 1-methylnaphthalen-2-ol from Step A (57.8 g, 365 mmol) and anhydrous MeOH (100 mL). The solution was chilled in an ice bath and sodium methanolate (83.1 mL, 365 mmol; 25 wt% in MeOH) was added dropwise under N₂ by addition funnel while stirring. The ice bath was removed and the reaction mixture was stirred for 30 minutes at ambient temperature, then concentrated in vacuo. Toluene (3 x 100 mL) was used to azeotrope residual MeOH. To the resulting solids was added iodomethane (203 mL, 3257 mmol), and the mixture was heated to reflux (oil bath temp = 50 °C) for 4 hours with stirring. Due to incomplete reaction, added toluene (300 mL) and DMF (50 mL) and increased the heat to 60 °C. 1H NMR analysis of the crude indicated the starting material had been consumed. The reaction was allowed to cool to ambient temperature, then concentrated in vacuo. The residue was partitioned between 1N NaOH (300 mL) and diethyl ether (300 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (2 x 100 mL). The combined organic phases were washed with water (200 mL), brine (200 mL), dried (MgSO₄), filtered, and concentrated to a dark oil (75 g). The crude material was purified by Biotage Flash 75L silica gel column, eluting with hexanes followed by 10% EtOAc/hexanes. Yield of 1,1-dimethylnaphthalen-2(1H)-one: 6.5 g (9%). The major by-product (which eluted from silica gel column with hexanes) was 2-methoxy-1-methylnaphthalene resulting from O-methylation.

[00936] Step C: Preparation of 1,1-dimethyl-1,2-dihydronaphthalen-2-ol: A round bottomed flask was charged with 1,1-dimethylnaphthalen-2(1H)-one (3.4 g, 20 mmol) and MeOH (50 mL). The solution was chilled in an ice bath and NaBH₄ (0.76 g, 20 mmol) was added in portions over 10 minutes. The reaction mixture was stirred for 10 minutes after addition was completion. The ice bath was removed and the reaction mixture was stirred for 30

minutes at ambient temperature. The reaction mixture was chilled in ice bath and carefully quenched with 2N NaOH (20 mL), and then partially concentrated mixture in vacuo. The residue was extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with brine (30 mL), dried (MgSO₄), filtered, and concentrated. Yield: 3.2 g (87%).

[00937] Step D: Preparation of 2-methoxy-1,1-dimethyl-1,2-dihydronaphthalene: A round bottomed flask was charged with 1,1-dimethyl-1,2-dihydronaphthalen-2-ol (1.74 g, 10 mmol) and anhydrous DMF (30 mL). The solution was chilled in an ice bath and sodium hydride (0.480 g, 12.0 mmol; 60% in oil) was added in portions over 10 minutes under a stream of N₂. The reaction mixture was stirred for 30 minutes in ice bath, then added iodomethane (0.93 mL, 15 mmol). The ice bath was removed and the reaction mixture was warmed to ambient temperature and stirred for 30 minutes. The reaction mixture was carefully quenched with saturated aqueous NH₄Cl (20 mL), and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic phases were washed with water (2 x 20 mL), brine (20 mL), dried (MgSO₄), filtered, and concentrated to provide the desired product. Yield: 1.98 g (95%).

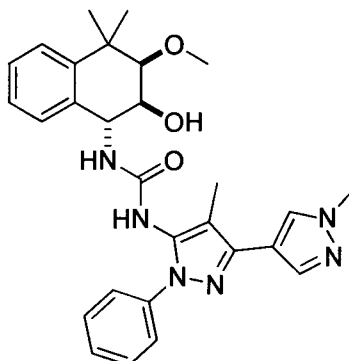
[00938] Step E: Preparation of (*r*-1a,*c*-2,*c*-7b)-2-methoxy-3,3-dimethyl-1a,2,3,7b-tetrahydronaphtho[1,2-*b*]oxirene: 2-methoxy-1,1-dimethyl-1,2-dihydronaphthalene (1.5 g, 8.0 mmol) and 1,2-dichloroethane (50 mL) were combined in a flask, and the flask was placed in an ice bath. Saturated aqueous NaHCO₃ (50 mL) was added, followed by addition of 3-chlorobenzoperoxoic acid (3.9 g, 16 mmol). The reaction mixture was allowed to warm to ambient temperature and was stirred overnight. The mixture was diluted with water (30 mL) and DCM (30 mL). The phases were separated and the aqueous phase was extracted with DCM (30 mL). The combined organic phases were washed with 2N NaOH (30 mL), dried (MgSO₄), filtered, and concentrated to provide the desired product. Yield: 1.8 g. Relative stereochemical assignments were based on NOE correlations between the gem-dimethyl hydrogen atoms and the saturated ring hydrogen atoms. The crude product carried into next step without purification.

[00939] Step F: Preparation of (*r*-1,*t*-2,*t*-3)-1-amino-3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol: Title compound prepared from (*r*-1a,*c*-2,*c*-7b)-2-methoxy-3,3-dimethyl-1a,2,3,7b-tetrahydronaphtho[1,2-*b*]oxirene (1.6 g, 7.83 mmol) according to the procedure described for Example 79, Step E. Yield: 538 mg (28%).

[00940] Step G: Preparation of 5-(3-((*r*-1,*t*-2,*t*-3)-2-hydroxy-3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ureido)-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide: Title compound prepared from (*r*-1,*t*-2,*t*-3)-1-amino-3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol from Step F (20 mg, 0.090 mmol) and 5-amino-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide (Intermediate 10; 21 mg, 0.090 mmol) according to the

procedure described for Example 79, Step F. Yield: 12 mg (27%). MS m/z (APCI-neg) $M-1 = 476.2$.

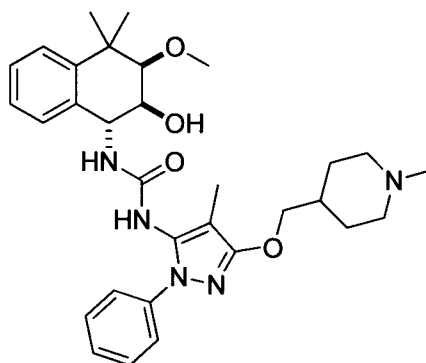
Example 86



1-((1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-((*r*-1,*t*-2,*t*-3)-2-hydroxy-3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)urea

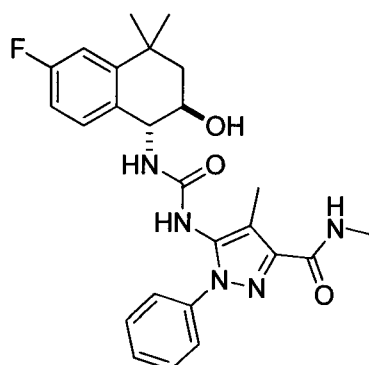
[00941] The title compound was prepared from (*r*-1,*t*-2,*t*-3)-1-amino-3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Example 85, Step F; 20 mg, 0.090 mmol) and 1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-amine (Intermediate 12, Step C; 23 mg, 0.090 mmol) according to the procedure described for Example 79, Step F. Yield: 10 mg (22%). MS m/z (APCI-pos) $M+1 = 501.2$.

Example 87



1-((*r*-1,*t*-2,*t*-3)-2-hydroxy-3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-((1-methylpiperidin-4-yl)methoxy)-1-phenyl-1H-pyrazol-5-yl)urea

[00942] The title compound was prepared from (*r*-1,*t*-2,*t*-3)-1-amino-3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Example 85, Step F; 20 mg, 0.090 mmol) and 4-methyl-3-((1-methylpiperidin-4-yl)methoxy)-1-phenyl-1H-pyrazol-5-amine (Intermediate Y3; 27 mg, 0.090 mmol) according to the procedure described for Example 79, Step F. Yield: 12 mg (24%). MS m/z (APCI-pos) $M+1 = 548.3$.

Example 88

5-(3-((1,2-*trans*)-6-fluoro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ureido)-
N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide

[00943] Step A: Preparation of 6-fluoro-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one: 5,5-Dimethyldihydrofuran-2(3H)-one (10.0 g, 87.6 mmol) and fluorobenzene (16.8 g, 175 mmol) were combined in a sealed tube and AlCl₃ (26.9 g, 202 mmol) added in small portions over 2 hours. The sealed tube was heated to 100 °C overnight with stirring. After cooling to ambient temperature, the reaction mixture was poured onto ice (75 mL) using more ice (50 mL) and EtOAc (100 mL) to help transfer. The phases were separated and the aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organic phases were washed with saturated aqueous NaHCO₃ (50 mL). The resulting emulsion was filtered through GF/F paper, rinsing with EtOAc. The phases were separated and the organic phase was dried (MgSO₄) filtered, and concentrated. The crude material was purified by Redi-Sep 330 silica gel column, eluting with a gradient of 5%-10% EtOAc/hexanes. ¹H NMR indicated a 70:30 ratio of two regioisomers: 6-fluoro-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one and 7-fluoro-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one, respectively. Yield of mixture: 2.7 g (11%). The mixture was used directly in the next step.

[00944] Step B: Preparation of 6-fluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol: A round bottomed flask was charged with a 70:30 mixture of the two regioisomers from step A (6-fluoro-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one and 7-fluoro-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one, respectively) (2.7 g, 14.0 mmol) and MeOH (30 mL). The solution was chilled in an ice bath. NaBH₄ (0.585 g, 15.5 mmol) was added in portions over a 15 minutes period, and the reaction mixture was stirred at ambient temperature for 2 hours. A majority of the solvent was removed in vacuo. The residue was partitioned between 2N NaOH (20 mL) and EtOAc (30 mL). The phases were separated and the aqueous phase was extracted with EtOAc (20 mL). The combined organic phases were washed with brine (20 mL), dried (MgSO₄), filtered, and concentrated. The two regioisomers were separated by RediSep 330 silica

gel column eluting with a gradient of 20%-30% EtOAc/hexanes. Yield of 6-fluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol: 1.48 g (49%). Yield of 7-fluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol: 601 mg (13%).

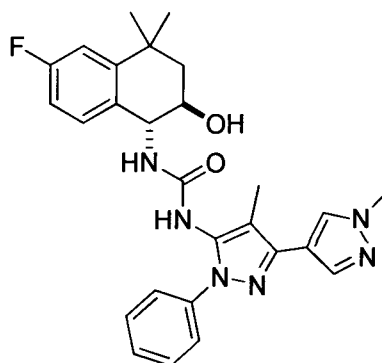
[00945] Step C: Preparation of 7-fluoro-1,1-dimethyl-1,2-dihydronaphthalene: A round bottomed flask was charged with 6-fluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (1.48 g, 7.62 mmol), 1,2-dichloroethane (20 mL) and 4-methylbenzenesulfonic acid hydrate (0.0725 g, 0.381 mmol). The reaction mixture was heated to 60 °C for 1 hour. The reaction mixture was cooled to ambient temperature, and then used directly into next step without workup or purification.

[00946] Step D: Preparation of 5-fluoro-3,3-dimethyl-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene: The reaction mixture containing 7-fluoro-1,1-dimethyl-1,2-dihydronaphthalene from Step C (1.34 g, 7.60 mmol) was stirred in an ice bath and saturated aqueous NaHCO₃ (20 mL) was added. 3-Chlorobenzoperoxoic acid (2.81 g, 11.4 mmol) was added and the reaction mixture was allowed to warm to ambient temperature, and stirring was continued overnight. The reaction mixture diluted with water (20 mL) and DCM (20 mL). The phases were separated and the aqueous phase was extracted with DCM (20 mL). The combined organic phases were washed with 2N NaOH (20 mL), dried (MgSO₄), filtered, and concentrated. The crude was used in the next step without purification. Yield: 1.49 g (71%).

[00947] Step E: Preparation of *trans*-1-amino-6-fluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol: A stainless steel bomb equipped with a Teflon insert and a stir bar was charged with 5-fluoro-3,3-dimethyl-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene (1.46 g, 7.60 mmol) using a few mL's of EtOH to transfer, and aqueous ammonium hydroxide (15 mL). The reaction mixture was heated to 90 °C in an oil bath overnight. The reaction mixture was cooled to ambient temperature and the bomb was placed in an ice bath before opening. The contents of the bomb were transferred to a round bottomed flask using EtOH, and then concentrated in vacuo. The crude mixture was partitioned between 1N aqueous HCl (15 mL) and diethyl ether (15 mL). The phases were separated and the organic phase was extracted with 1N HCl (5 mL). The combined aqueous phases were extracted with diethyl ether (20 mL). The aqueous phases were chilled in an ice bath and basified with NaOH pellets (added a few at a time with sonication to dissolve, until pH was >12). The product precipitated out of basic aqueous phase. The product was extracted with 20% EtOAc in diethyl ether (2 x 20 mL). The combined organic phases were dried (MgSO₄), filtered, and concentrated in vacuo to provide the crude desired product. Yield: 572 mg (32%). The crude carried was used directly in the next step without purification.

[00948] Step F: Preparation of 5-(3-((1,2-*trans*)-6-fluoro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ureido)-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide: The title compound was prepared from *trans*-1-amino-6-fluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (20 mg, 0.096 mmol) and 5-amino-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide (Intermediate 10, 22 mg, 0.096 mmol) according to the procedure for Example 79, Step F. Yield: 12 mg (26%). MS *m/z* (APCI-neg) *M*-1 = 464.2.

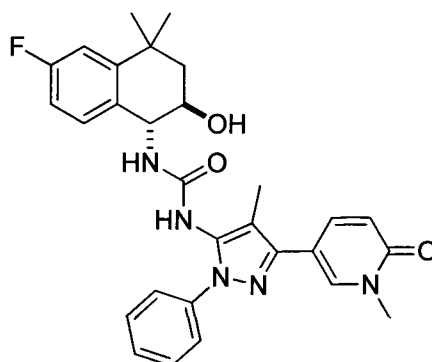
Example 89



1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-((1,2-*trans*)-6-fluoro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)urea

[00949] The title compound was prepared from *trans*-1-amino-6-fluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Example 88, Step E; 20 mg, 0.096 mmol) and 1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-amine (Intermediate 12, 24 mg, 0.096 mmol) according to the procedure for Example 79, Step F. Yield: 9 mg (19%). MS *m/z* (APCI-pos) *M*+1 = 489.2.

Example 90

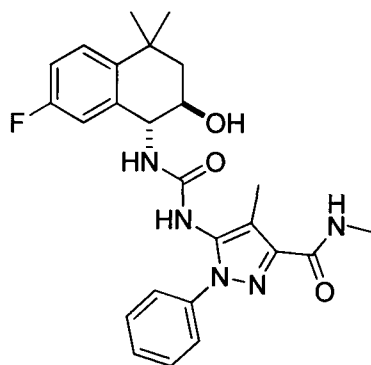


1-((1,2-*trans*)-6-fluoro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)urea

[00950] The title compound was prepared from *trans*-1-amino-6-fluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Example 88, Step E; 20 mg, 0.096 mmol) and 5-(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)-1-methylpyridin-2(1H)-one (Intermediate 7, 27 mg, 0.096 mmol) according to the procedure for Example 79, Step F. Yield: 11 mg (22%). MS *m/z* (APCI-

neg) M-1 = 514.2.

Example 91



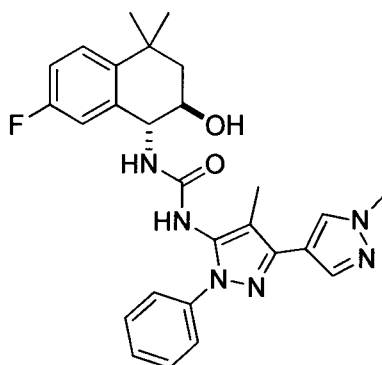
5-(3-((1,2-*trans*)-7-fluoro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ureido)-
N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide

[00951] Step A: Preparation of 6-fluoro-1,1-dimethyl-1,2-dihydronaphthalene: Prepared from 7-fluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (Example 88, Step B; 601 mg, 3.09 mmol) according to the procedure for Example 88, Step C. Crude reaction mixture was carried forward into next step without workup or purification.

[00952] Step B: Preparation of 6-fluoro-3,3-dimethyl-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene: Prepared from the crude reaction mixture containing 6-fluoro-1,1-dimethyl-1,2-dihydronaphthalene from Step A according to the procedure for Example 88, Step D. Purified crude by Red-Sep 120 silica gel column eluting with a gradient of 5%-10% EtOAc/hexanes. Yield: 110 mg (17%). Structural assignment was based on ¹H NMR NOE correlations.

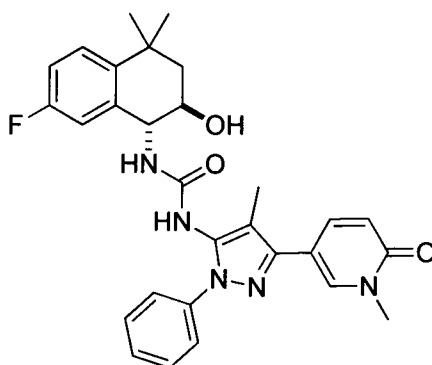
[00953] Step C: Preparation of *trans*-1-amino-7-fluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol: Prepared from 6-fluoro-3,3-dimethyl-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene (110 mg, 0.572 mmol) according to the procedure for Example 88, Step E. Yield: 93 mg (70%).

[00954] Step D: Preparation of 5-(3-((1,2-*trans*)-7-fluoro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ureido)-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide: Prepared from *trans*-1-amino-7-fluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (20 mg, 0.096 mmol) and 5-amino-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide (Intermediate 10, 22 mg, 0.096 mmol) according to the procedure for Example 7, Step F. Yield: 9 mg (20%). MS *m/z* (APCI-neg) M-1 = 464.2.

Example 92

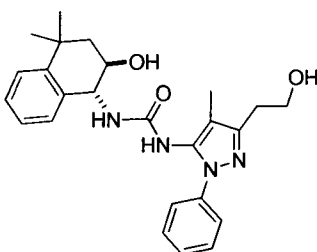
1-((1,2-*trans*)-7-fluoro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-((1,4-dimethyl-1-phenyl-1H-[3,4'-bipyrazol]-5-yl)urea

[00955] The title compound was prepared from *trans*-1-amino-7-fluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Example 91, Step C; 20 mg, 0.096 mmol) and 1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-amine (Intermediate 12, 24 mg, 0.096 mmol) according to the procedure for Example 79, Step F. Yield: 12 mg (24%). MS *m/z* (APCI-pos) *M*+1 = 489.2.

Example 93

1-((1,2-*trans*)-7-fluoro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)urea

[00956] The title compound was prepared from *trans*-1-amino-7-fluoro-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Example 91, Step C; 20 mg, 0.096 mmol) and 5-(5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)-1-methylpyridin-2(1H)-one (Intermediate 7, 27 mg, 0.096 mmol) according to the procedure for Example 79, Step F. Yield: 10 mg (19%). MS *m/z* (APCI-neg) *M*-1 = 514.2.

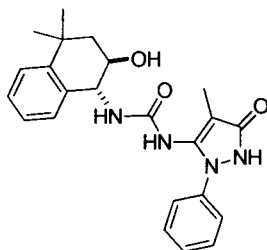
Example 94

1-(*trans*-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(2-hydroxyethyl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea

[00957] Step A: Preparation of 1-(3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-(*trans*-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)urea: A mixture of phenyl (3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)carbamate (13.4 mg, 0.03 mmol), *trans*-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Intermediate X1, 12.5 mg, 0.033 mmol) and triethylamine (15.0 mg, 0.15 mmol) were combined in 0.2 mL of DMF and stirred at ambient temperature for 1 hour. The mixture was loaded onto a samplet and purified by reverse-phase column chromatography, eluting with 0-70 % acetonitrile/water, to afford the title compound (7.5 mg, 0.014 mmol, 46 % yield). MS (apci) m/z = 549.3 (M+H).

[00958] Step B: Preparation of 1-(*trans*-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(2-hydroxyethyl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea: 1-(3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-(*trans*-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)urea (7.0 mg, 0.0128 mmol) and HCl (21.3 μ L, 0.128 mmol) (in IPA) were combined in 1 mL of DCM and stirred at ambient temperature for 1 hour. The mixture was concentrated and purified by reverse-phase column chromatography, eluting with 0-60 % acetonitrile/water, to afford the title compound (2.3 mg, 0.00529 mmol, 41.5 % yield). MS (apci) m/z = 435.2 (M+H).

Example 95

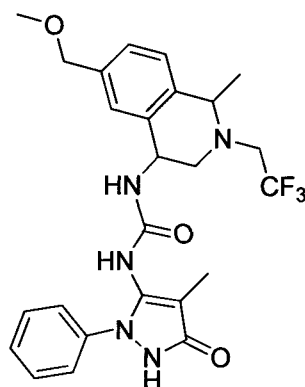


1-(*trans*-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-5-oxo-2-phenyl-2,5-dihydro-1H-pyrazol-3-yl)urea

[00959] CDI (565.6 mg, 3.488 mmol), 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one (Intermediate 2, Step A, 300 mg, 1.586 mmol) and NEt_3 (497.2 μ L, 3.567 mmol) were combined in 3 mL of DMF and stirred at ambient temperature overnight. Additional CDI (200 mg) was added and the reaction stirred for 3 days. 1 mL of the resultant solution was added to a solution of *trans*-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Intermediate X1, 50 mg, 0.26 mmol) and NEt_3 (109 μ L, 0.78 mmol) in 0.2 mL of DMF. The mixture was and stirred at ambient temperature for 1 hour, loaded onto a samplet and purified by reverse-phase column

chromatography, eluting with 0-70 % acetonitrile/water, to afford the title compound (36 mg, 0.089 mmol, 34 % yield). MS (apci) m/z = 407.2 (M+H).

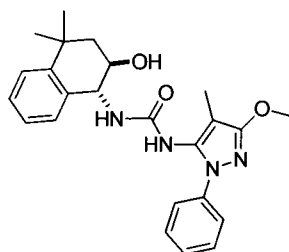
Example 96



1-(6-(methoxymethyl)-1-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)-3-(4-methyl-5-oxo-2-phenyl-2,5-dihydro-1H-pyrazol-3-yl)urea

[00960] CDI (565.6 mg, 3.488 mmol), 5-amino-4-methyl-1-phenyl-1H-pyrazol-3(2H)-one (Intermediate 2, Step A, 300 mg, 1.586 mmol) and NEt_3 (497 μL , 3.567 mmol) were combined in 3 mL of DMF and stirred at ambient temperature overnight. Additional CDI (200 mg) was added and the reaction stirred for 3 days. 0.1 mL of the resultant solution were added to a solution of 6-(methoxymethyl)-1-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-amine (10 mg, 0.035 mmol), and NEt_3 (11 μL , 0.078 mmol) in 0.1 mL of DMF. The mixture was and stirred at ambient temperature for 1 hour, loaded onto a samplet and purified by reverse-phase column chromatography, eluting with 0-50 % acetonitrile/water, to afford the title compound (6.9 mg, 0.014 mmol, 40 % yield). MS (apci) m/z = 504.2 (M+H).

Example 97

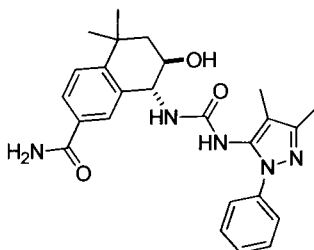


1-(trans-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea

[00961] 1-(trans-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-5-oxo-2-phenyl-2,5-dihydro-1H-pyrazol-3-yl)urea (Example 95, 77 mg, 0.19 mmol) was dissolved in DCM (10 mL) and MeOH (10 mL) and a solution of TMS-Diazomethane in hexanes (142 μL , 0.28 mmol) was added dropwise. The reaction was stirred at ambient temperature for 1 hour, concentrated and purified by reverse-phase column chromatography,

eluting with 0-70 % acetonitrile/water, to afford the title product as white solid (40 mg, 0.095 mmol, 50 % yield) (peak 2, MS (apci) m/z = 421.1 (M+H)) and regioisomeric side-product 1-(1,4-dimethyl-5-oxo-2-phenyl-2,5-dihydro-1H-pyrazol-3-yl)-3-(*trans*-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)urea (11 mg, 0.026 mmol, 14 % yield) (peak 1, MS (apci) m/z = 421.2 (M+H)).

Example 98



trans-8-(3-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)ureido)-7-hydroxy-5,5-dimethyl-5,6,7,8-tetrahydronaphthalene-2-carboxamide

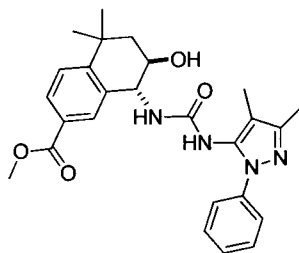
[00962] Step A: Preparation of methyl 3,3-dimethyl-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene-6-carboxylate: 6-bromo-1,1-dimethyl-1,2-dihydronaphthalene (200 mg, 0.843 mmol) (prepared as described in Step B, Intermediate X4) was dissolved in THF (10 mL) and cooled to -78 °C. A 1.7N solution of *tert*-BuLi in pentane (1.141 mL, 1.94 mmol) was added dropwise and the reaction was stirred at -78 °C for 20 minutes. Methyl chloroformate (130 μ L, 1.69 mmol) was added and the reaction was allowed to warm to ambient temperature overnight, quenched with brine (10 mL) and extracted with EtOAc (2x25 mL). The combined organic extracts were filtered through phase separator paper and concentrated. The crude product was purified by silica gel column, eluting with 0-10% EtOAc/hexanes, to afford methyl 5,5-dimethyl-5,6-dihydronaphthalene-2-carboxylate (69 mg, 0.319 mmol, 37.8 % yield) which was dissolved in DCM (5 mL) and NaHCO₃ (saturated aqueous, 5 mL) and stirred at 0 °C. 3-chlorobenzoperoxoic acid (87 mg, 0.35 mmol) was added and the reaction was allowed to warm to ambient temperature overnight. The mixture was extracted with several portions of DCM, and the combined organic extracts were filtered through phase separator paper and concentrated to afford methyl 3,3-dimethyl-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene-6-carboxylate (66 mg, 0.28 mmol, 89 % yield). ¹H NMR (CDCl₃) 8.10-8.12 (m, 1H), 7.96-8.00 (m, 1H), 7.41-7.46 (m, 1H), 3.90-3.95 (m, 4H), 3.72-3.77 (m, 1H), 2.18-2.28 (s, 6H), 1.18-1.90 (m, 1H), 1.37 (s, 1H), 1.32 (s, 1H) ppm.

[00963] Step B: Preparation of "Solution A": CDI (144 mg, 0.534 mmol), 3,4-dimethyl-1-phenyl-1H-pyrazol-5-amine (100 mg, 0.534 mmol) and NEt₃ (250 μ L, 1.79 mmol) were combined in 1.75 mL of DMF and stirred at ambient temperature over the weekend. The

resultant solution was used in the procedure described below.

[00964] Step C: Preparation of *trans*-8-(3-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)ureido)-7-hydroxy-5,5-dimethyl-5,6,7,8-tetrahydronaphthalene-2-carboxamide: methyl 3,3-dimethyl-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene-6-carboxylate (66 mg, 0.2841 mmol) and concentrated ammonium hydroxide (3.161 mL, 28.41 mmol) were combined in a sealed vessel and stirred in a 50 °C sand bath for 5 hour. The reaction was cooled, concentrated and dissolved in DMF (1 mL). 1052 μ L of "Solution A" were added followed by NEt₃ (196 μ L, 1.40 mmol). The reaction was stirred at ambient temperature for 1 hour, loaded onto a samplet and purified by reverse-phase column chromatography, eluting with 0-70 % acetonitrile/water, to afford the title product as white solid (4.1 mg, 0.00916 mmol, 3.26 % yield) (peak 2, MS (apci) m/z = 448.3 (M+H)), as well as a side-product *trans*-8-(3-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)ureido)-7-hydroxy-5,5-dimethyl-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (11.3 mg, 0.0252 mmol, 8.97 % yield) (peak 1, (MS (apci) m/z = 449.2 (M+H)).

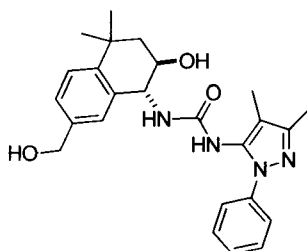
Example 99



trans-methyl 8-(3-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)ureido)-7-hydroxy-5,5-dimethyl-5,6,7,8-tetrahydronaphthalene-2-carboxylate

[00965] *trans*-8-(3-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)ureido)-7-hydroxy-5,5-dimethyl-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (Example 98 Side Product, 5.0 mg, 0.011 mmol) was dissolved in MeOH (0.5 mL) and DCM (0.5 mL) and a 2M solution of TMS-Diazomethane in hexanes (11.1 μ L, 0.022 mmol) was added. The reaction was stirred for 1 hour, formic acid (1 drop) was added and the reaction was concentrated to afford *trans*-methyl 8-(3-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)ureido)-7-hydroxy-5,5-dimethyl-5,6,7,8-tetrahydronaphthalene-2-carboxylate (5.10 mg, 0.011 mmol, 98.9 % yield). MS (apci) m/z = 463.3 (M+H).

Example 100



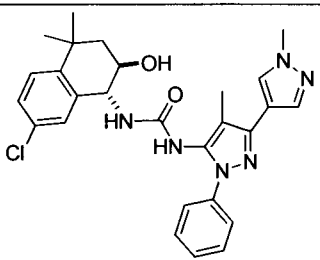
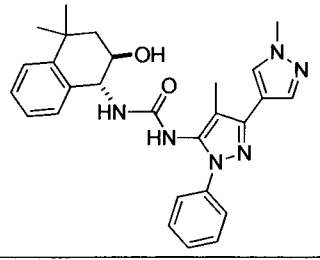
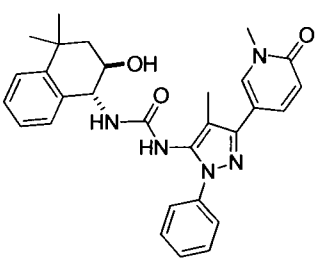
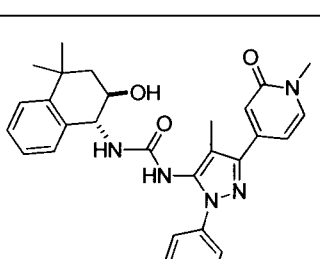
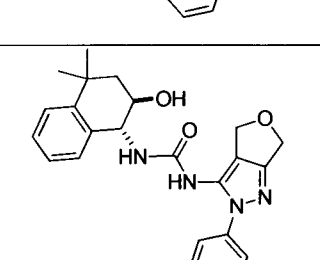
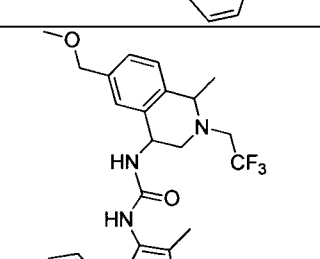
(1-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)-3-(*trans*-2-hydroxy-7-(hydroxymethyl)-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)urea

[00966] *trans*-methyl 8-(3-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)ureido)-7-hydroxy-5,5-dimethyl-5,6,7,8-tetrahydronaphthalene-2-carboxylate (10 mg, 0.0216 mmol) was dissolved in THF (1 mL) and cooled to 0 °C. A 1M solution of LiAlH₄ in THF (21.6 µl, 0.0216 mmol) was added and the reaction was allowed to warm to ambient temperature overnight. Sodium sulfate decahydrate (69 mg, 0.22 mmol) was added and the reaction was stirred for 2 hours, filtered and concentrated. The crude product was purified by reverse-phase column chromatography, eluting with 0-60 % acetonitrile/water, to afford 1-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)-3-(*trans*-2-hydroxy-7-(hydroxymethyl)-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)urea (4.2 mg, 0.01 mmol, 44.7 % yield). MS (apci) *m/z* = 435.2 (M+H).

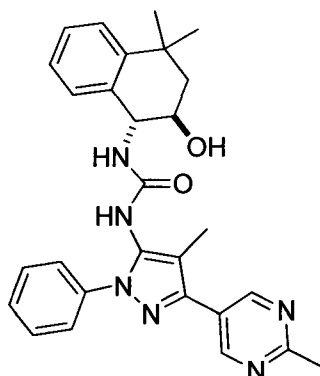
[00967] The compounds listed in Table 3 were prepared in a similar fashion as described in Example 1, replacing 1,2,3,4-tetrahydronaphthalen-1-amine and phenyl 1',4-dimethyl-1-phenyl-1H,1'H-3,4'-bipyrazol-5-ylcarbamate with the appropriate amine and phenylcarbamate starting materials, respectively.

Table 3

Example #	Structure	Name	MS (apci) <i>m/z</i>
101		1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(<i>trans</i> -2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)urea	443.2 (M+H)
102		1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(<i>trans</i> -2-hydroxy-7-(methoxymethyl)-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)urea	515.3
103		(S)-1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(6-fluoro-1,2,3,4-tetrahydronaphthalen-1-yl)urea	445.2 (M+H)

Example #	Structure	Name	MS (apci) m/z
104		1-(<i>trans</i> -7-chloro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(1',4'-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea	505.3 (M+H)
105		1-(1',4'-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(<i>trans</i> -2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)urea	471.2 (M+H)
106		1-(<i>trans</i> -2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)urea	496.2 (M-H)
107		1-(<i>trans</i> -2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-1-phenyl-1H-pyrazol-5-yl)urea	496.2 (M-H)
108		1-(<i>trans</i> -2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(2-phenyl-4,6-dihydro-2H-furo[3,4-c]pyrazol-3-yl)urea	517.2 (M-H)
109		1-(1',4'-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(6-(methoxymethyl)-1-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)urea	568.3 (M+H)

Example #	Structure	Name	MS (apci) m/z
110		5-(3-(6-(methoxymethyl)-1-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)ureido)-4-methyl-1-phenyl-1H-pyrazole-3-carboxamide	529.2 (M-H)
111		1-(6-(methoxymethyl)-1-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)-3-(4-methyl-3-(1-methyl-1H-imidazol-4-yl)-1-phenyl-1H-pyrazol-5-yl)urea	568.2 (M+H)
112		1-(6-bromothiochroman-4-yl)-3-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea	523.0 525.0 (M+H)
113		1-(6-bromo-1,1-dioxidothiochroman-4-yl)-3-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea	555.1 557.1 (M+H)
114		1-(6-bromoisothiochroman-4-yl)-3-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea	521.1 523.1 (M-H)
115		1-(6-bromo-2,2-dioxidoisothiochroman-4-yl)-3-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)urea	553.0 555.0 (M-H)
116		1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)urea	522.1 (M-H)

Example 117

1-((1,2-*trans*)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-yl)urea

[00968] A mixture of CDI (61.1 mg, 0.226 mmol) (estimated 60% potent based on previous experiments), 4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-amine (Intermediate Y4, 60 mg, 0.226 mmol) and NEt₃ (99.3 μ L, 0.712 mmol) were combined in DMF (0.9 mL) and stirred at ambient temperature for 48 hours. An aliquot of this solution containing 5-(5-isocyanato-4-methyl-1-phenyl-1H-pyrazol-3-yl)-2-methylpyrimidine (approx. 0.22 M, 108 μ L, 0.024 mmol) was diluted with DMF (0.2 mL), followed by addition of *trans*-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Intermediate X1, 5 mg, 0.026 mmol) and triethylamine (12 mg, 0.12 mmol). After stirring at ambient temperature for 1 hour, the mixture was directly purified by reverse phase chromatography (C18, 0-70% acetonitrile/water) to afford the title product as white solid (4.3 mg, 37 % yield). MS (apci) m/z = 483.3 (M+H).

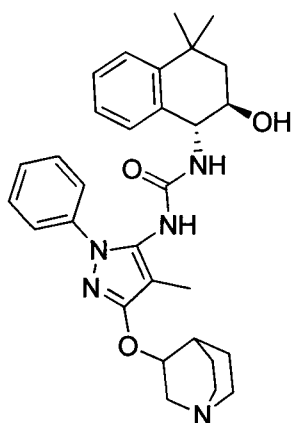
[00969] The compounds listed in Table 4 were prepared in a similar fashion as described in Example 117, replacing 4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-amine and *trans*-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol with the appropriate aminopyrazole and amine starting materials, respectively.

Table 4

Example #	Structure	Name	MS (apci) m/z
118		1-(<i>trans</i> -2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-yl)urea	455.2 (M+H)

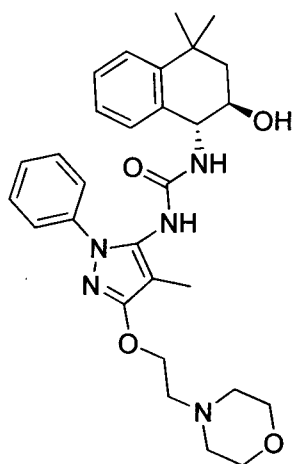
Example #	Structure	Name	MS (apci) m/z
119		1-(<i>trans</i> -2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(2-methoxypyrimidin-5-yl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea	471.2 (M+H)
120		5-(3-(<i>trans</i> -2-hydroxy-7-(methoxymethyl)-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ureido)-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide	490.3 (M-H)
121		1-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)-3-(<i>trans</i> -2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)urea	377.2 (M+H)
122		1-(<i>trans</i> -2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-((1-methylpiperidin-4-yl)methoxy)-1-phenyl-1H-pyrazol-5-yl)urea	518.3 (M+H)
123		1-(<i>trans</i> -2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-((1-methylpiperidin-4-yl)methoxy)-1-phenyl-1H-pyrazol-5-yl)urea	490.3 (M+H)
124		5-(3-(<i>trans</i> -2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ureido)-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide	448.2 (M+H)
125		5-(3-(<i>trans</i> -7-chloro-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ureido)-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide	482.2 (M+H)

Example #	Structure	Name	MS (apci) m/z
126		1-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)-3-(<i>trans</i> -6-hydroxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)urea	391.2 (M+H)
127		1-(<i>trans</i> -6-hydroxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)-3-(4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-yl)urea	469.2 (M+H)
128		1-(<i>trans</i> -6-hydroxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)-3-(3-(2-methoxypyrimidin-5-yl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea	485.2 (M+H)
129		5-(3-(6-(methoxymethyl)-1-methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)ureido)-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide	543.2 (M-H)
130		1-(4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-yl)-3-(1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)urea	534.2 (M-H)
131		1-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)-3-(1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)urea	458.2 (M+H)

Example 132

1-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-1-phenyl-3-(quinuclidin-3-yloxy)-1H-pyrazol-5-yl)urea

[00970] To a solution of 4-methyl-1-phenyl-3-(quinuclidin-3-yloxy)-1H-pyrazol-5-amine (0.051 g, 0.17 mmol) in DriSolve DCM (1.7 mL) cooled in an ice-water bath was added triphosgene (0.0304 g, 0.10 mmol) followed by DIEA (0.089 mL, 0.51 mmol). It was stirred at 0 °C for 1 hour, then (1R,2R)-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Intermediate X2, 0.033 g, 0.17 mmol) was added in one portion. The reaction mixture was allowed to warm to ambient temperature and was stirred for 1 hour. The reaction mixture was concentrated and directly purified by reverse phase chromatography (C18, 5 to 70% methanol/water) to yield the product as white solid (28.3 mg, 32% yield). MS (apci) m/z = 516.3 (M+H).

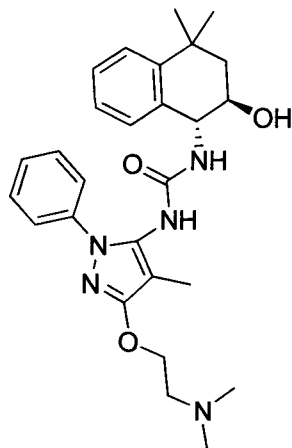
Example 133

1-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-(2-morpholinoethoxy)-1-phenyl-1H-pyrazol-5-yl)urea

[00971] The title product was prepared as described for Example 132, using 4-methyl-3-(2-morpholinoethoxy)-1-phenyl-1H-pyrazol-5-amine (Intermediate P141, 0.025 g, 0.0827 mmol) instead of 4-methyl-1-phenyl-3-(quinuclidin-3-yloxy)-1H-pyrazol-5-amine. The crude

material was purified via reverse-phase chromatography (C18, 5 to 50% acetonitrile/water) to provide the title compound as white solid (24 mg, 55% yield. MS (apci) m/z = 520.3 (M+H).

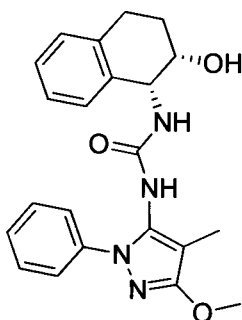
Example 134



1-(3-(2-(dimethylamino)ethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)urea

[00972] The title product was prepared as described for Example 132, using 3-(2-(dimethylamino)ethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-amine (Intermediate Y6, 0.030 g, 0.115 mmol) instead of 4-methyl-1-phenyl-3-(quinuclidin-3-yloxy)-1H-pyrazol-5-amine. The product was isolated via reverse-phase chromatography (C18, 5 to 50% acetonitrile/water) as white solid (10 mg, 18% yield. MS (apci) m/z = 478.3 (M+H).

Example 135



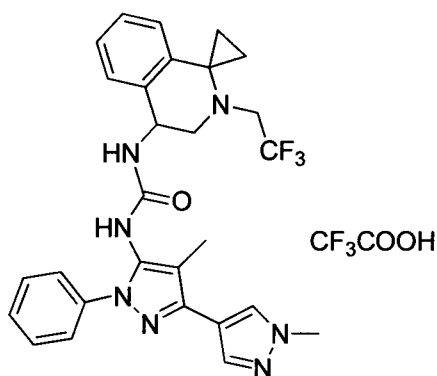
1-((1R,2S)-2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea

[00973] Step 1. Synthesis of tert-butyl ((1R,2S)-2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)carbamate. Tert-butyl carbamate (363 mg, 3.10 mmol) was dissolved in 1-propanol (4 mL) in a 20-mL scintillation vial equipped with a magnetic stir bar. To this solution was added a freshly prepared solution of sodium hydroxide (122 mg, 3.05 mmol) in water (7.5 mL) while stirring, followed by freshly prepared tert-butyl hypochlorite (331 mg, 3.05 mmol, 0.35 mL). A solution of the ligand (DHQD)2PHAL (38.9 mg, 0.0499 mmol) in 1-propanol (3.5 mL) was added to provide a clear colorless solution. The reaction vessel was immersed in a ambient-

temperature water bath and stirred for a few minutes, and then 1,2-dihydronaphthalene (130 mg, 0.999 mmol) was added, followed by K₂OsO₄·2H₂O (14.7 mg, 0.0399 mmol) in one portion. After 1 hour, the reaction mixture was diluted with EtOAc (7 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water and brine, dried (Na₂SO₄), filtered and concentrated. The crude material was purified first by silica chromatography (10% acetone in hexanes) and then by reverse-phase chromatography (C18, 5 to 65% MeOH/water) to yield the product as colorless glassy solid (50 mg, 19% yield).

[00974] Step 2. Synthesis of 1-((1R,2S)-2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea. Tert-butyl ((1R,2S)-2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)carbamate (25 mg, 0.095 mmol) was treated with 1:1 v/v TFA/DCM (1 mL) at ambient temperature for 1 hour, then concentrated. The residue was taken up in DCM (2 mL) and washed with 1N NaOH and brine (1 mL each), and the organic phase was separated and concentrated. The residue was taken up in IPA (0.4 mL), followed by addition of phenyl (3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)carbamate (intermediate 3, 31 mg, 0.095 mmol) in one portion. The resulting milky suspension was warmed up briefly with a heat gun to obtain a clear solution and then heated at 50 °C for 3 hours, then at reflux for 1 hour. After cooling to ambient temperature, the reaction mixture was filtered, rinsed with ice-cold IPA first followed by ether (0.5 mL each), yielding the product as white solid (10 mg, 27% yield). MS (apci) m/z = 393.2 (M+H).

Example 136



1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(2'-(2,2,2-trifluoroethyl)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-isoquinolin]-4'-yl)urea trifluoroacetate

[00975] Step A: Preparation of N-(2,2-dimethoxyethyl)-1-phenylcyclopropanamine: A solution of 1-phenylcyclopropanamine (3.14 g, 23.6 mmol) in anhydrous DCM (100 mL) was treated with 2,2-dimethoxyacetaldehyde (4.09 g, 60% in water, 23.6 mmol) followed by acetic acid (135 µL, 2.36 mmol) and MgSO₄ (6.0 g). The mixture was stirred at ambient temperature

for 16 hours then filtered, washed with a small amount of DCM and the filtrate treated with $\text{Na}(\text{OAc})_3\text{BH}$ (5.5 g, 25.9 mmol). After stirring at ambient temperature for 16 hours, the mixture was treated with ice and 2N NaOH and then extracted with DCM (3 x 30 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by silica column chromatography eluting with 4:1 hexanes:EtOAc, to afford N-(2,2-dimethoxyethyl)-1-phenylcyclopropanamine (2.31 g, 44% yield) as a pale yellow oil. MS (EI) $m/z = 220.05$ (M-H).

[00976] Step B: Preparation of N-(2,2-dimethoxyethyl)-1-phenyl-N-(2,2,2-trifluoroethyl)cyclopropanamine: To a solution of N-(2,2-dimethoxyethyl)-1-phenylcyclopropanamine (2.31 g, 10.44 mmol) in anhydrous DMF (10 mL) was added 2,2,2-trifluoroethyltriflate (3.76 mL, 26.1 mmol) followed by Et_3N (6.36 mL, 36.5 mmol). The mixture was heated in a sealed vial at 45 °C for 16 hours, then treated with 2,2,2-trifluoroethyltriflate (5 mL) and stirred at 65 °C for 6 hours. The cooled mixture was partitioned between water (50 mL) and EtOAc (50 mL) and the aqueous layer extracted with EtOAc (2 x 30 mL). The combined organic phases were washed with water (4 x 20 mL) and brine (20 mL) then dried over Na_2SO_4 , filtered and concentrated. The residue was purified by silica column chromatography eluting with 9:1 to 4:1 hexanes:EtOAc, to afford N-(2,2-dimethoxyethyl)-1-phenyl-N-(2,2,2-trifluoroethyl)cyclopropanamine (934 mg, 29% yield) as a pale yellow oil. MS (apci) $m/z = 303.2$ (M+H).

[00977] Step C: Preparation of 2'-(2,2,2-trifluoroethyl)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-isoquinolin]-4'-ol: N-(2,2-dimethoxyethyl)-1-phenyl-N-(2,2,2-trifluoroethyl)cyclopropanamine (934 mg, 3.08 mmol) was treated with perchloric acid (3.72 mL, 61.6 mmol) and stirred at ambient temperature for 3 hours. The mixture was treated with ice and 2N NaOH, stirred for 1 hour then extracted with DCM (3 x 20 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by silica column chromatography eluting with 9:1 hexanes:EtOAc, to afford 2'-(2,2,2-trifluoroethyl)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-isoquinolin]-4'-ol (328 mg, 41% yield) as a cream, crystalline solid. MS (apci) $m/z = 258.1$ (M+H).

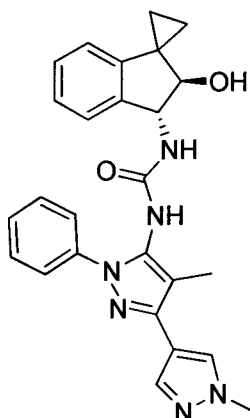
[00978] Step D: Preparation of 4'-chloro-2'-(2,2,2-trifluoroethyl)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-isoquinoline]: To a solution of 2'-(2,2,2-trifluoroethyl)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-isoquinolin]-4'-ol (50 mg, 0.19 mmol) in anhydrous DCM (1 mL) at 0 °C was added mesyl chloride (17 μL , 0.21 mmol) followed by DIEA (68 μL , 0.39 mmol). The mixture was stirred at ambient temperature for 2 hours then partitioned between water (10 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (2 x 5 mL) and the combined

organic phases were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated. The residue was dissolved in DCM (10 mL) and concentrated to afford 4'-chloro-2'-(2,2,2-trifluoroethyl)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-isoquinoline] (50 mg, 93% yield) as a pale yellow oil. MS (EI) m/z = 275.89 (M+H).

[00979] Step E: Preparation of 4'-azido-2'-(2,2,2-trifluoroethyl)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-isoquinoline]: To a solution of 4'-chloro-2'-(2,2,2-trifluoroethyl)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-isoquinoline] (50 mg, 0.18 mmol) in anhydrous DMF (1 mL) was added sodium azide (24 mg, 0.36 mmol). The mixture was stirred at 65 °C for 3 hours then cooled and partitioned between water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic phases were washed with water (4 x 5 mL) and brine (5 mL) then dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography eluting with 9:1 hexanes:EtOAc, to afford 4'-azido-2'-(2,2,2-trifluoroethyl)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-isoquinoline] (19 mg, 37% yield) as a colorless oil. MS (apci) m/z = 255.1 (M[-N₂]+H).

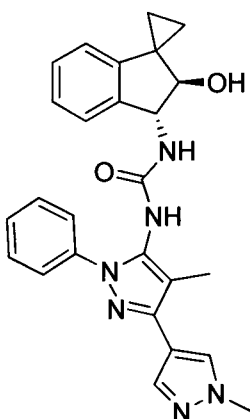
[00980] Step F: Preparation of 2'-(2,2,2-trifluoroethyl)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-isoquinolin]-4'-amine: A solution of 4'-azido-2'-(2,2,2-trifluoroethyl)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-isoquinoline] (19 mg, 0.067 mmol) in methanol (5 mL) was treated with 5% Pd/C (wet, Degussa type, 2 mg) and stirred under a hydrogen balloon atmosphere for 3 hours. The mixture was filtered through GF paper and the filtrate concentrated to afford 2'-(2,2,2-trifluoroethyl)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-isoquinolin]-4'-amine (14 mg, 81% yield) as a colorless gum. MS (apci) m/z = 257.1 (M+H).

[00981] Step G: Preparation of 1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(2'-(2,2,2-trifluoroethyl)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-isoquinolin]-4'-yl)urea 2,2,2-trifluoroacetate: To a solution of 2'-(2,2,2-trifluoroethyl)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-isoquinolin]-4'-amine (14 mg, 0.055 mmol) in anhydrous DCM (1 mL) was added phenyl (1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)carbamate [Intermediate 13] (18 mg, 0.50 mmol) followed by DIEA (26 µL, 0.15 mmol). The mixture was stirred at ambient temperature for 16 hours then partitioned between water (10 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (2 x 5 mL) and the combined organic phases were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica column chromatography eluting with 2% MeOH/DCM, then by reverse-phase HPLC (5-95% ACN/water/0.1% TFA over 20 minutes) to afford the title compound TFA salt (3.7 mg, 11% yield) as a white solid. MS (apci) m/z = 534.2 (M-H).

Example 137

1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-((2'R,3'R)-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)urea

[00982] To (2'R,3'R)-3'-amino-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-ol (Intermediate X9, 10.6 mg, 0.0605 mmol) were added iPrOH (0.6 mL) then phenyl (1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)carbamate (Intermediate 13, 22.6 mg, 0.0605 mmol). The reaction mixture was heated to 70 °C for 15 minutes, then was allowed to cool slowly to ambient temperature. The suspension was filtered, rinsed with Et₂O (4 x 1 mL), and the solid was collected to afford the product as a white solid (20.4 mg, 74% yield). MS (apci) m/z = 455.2 (M+H).

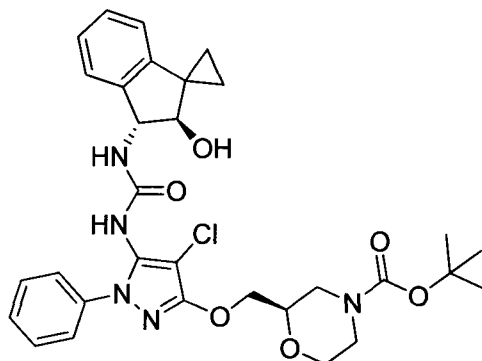
Example 138

1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-((2'S,3'S)-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)urea

[00983] To (2'S,3'S)-3'-amino-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2'-ol (Intermediate X10, 18.4 mg, 0.105 mmol) were added iPrOH (1 mL) then phenyl (1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)carbamate (Intermediate 13, 39.2 mg, 0.105 mmol). The reaction mixture was heated to 70 °C for 15 minutes and then allowed to cool slowly to ambient temperature. The suspension was filtered, rinsed with Et₂O (4 x 1 mL), and the solid was

collected to afford the product as a white solid (37.4 mg, 78% yield). MS (apci) m/z = 455.2 (M+H).

Example 139



(R)-tert-butyl 2-(((4-chloro-5-(3-((2'R,3'R)-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)ureido)-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate

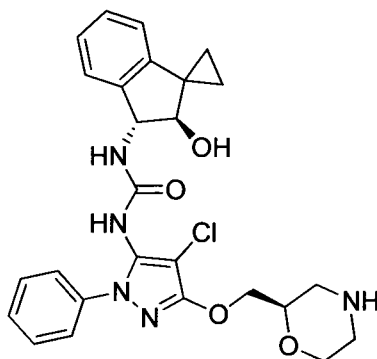
[00984] Step A: Preparation of (R)-tert-butyl 2-(((5-((phenoxycarbonyl)amino)-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate: To a solution of (R)-tert-butyl 2-(((5-amino-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate (Intermediate Y8, 200 mg, 0.534 mmol) in EtOAc (5 mL) was added aqueous NaOH (2M, 0.534 mL, 1.068 mmol) then phenyl chloroformate (100 μ L, 0.8012 mmol). The reaction mixture was stirred at ambient temperature for 23 hours and then transferred to separatory funnel with EtOAc (25 mL). The phases were separated, and the organic phase was washed with H₂O (25 mL), brine (25 mL), dried (MgSO₄), filtered and concentrated to a thick syrup. Added hexanes (10 mL), sonicated, decanted hexanes, then dried under high vacuum to afford the product as a brown solid (242 mg, 92% yield). MS (apci) m/z = 495.2 (M+H).

[00985] Step B: Preparation of (R)-tert-butyl 2-(((4-chloro-5-((phenoxycarbonyl)amino)-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate: To a solution of (R)-tert-butyl 2-(((5-((phenoxycarbonyl)amino)-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate (242 mg, 0.489 mmol) in DCM (5 mL) were added NCS (85 mg, 0.636 mmol) and PPTS (12.3 mg, 0.049 mmol). The reaction mixture was stirred at ambient temperature for 6 days, then was diluted with H₂O (10 mL), extracted with DCM (3 x 10 mL), and the combined organic phases were dried (MgSO₄), filtered, and concentrated. The crude oil was purified by silica column chromatography, eluting with 0-30% acetone/hexanes, to afford the product as an orange solid (153 mg, 66% yield). MS (apci) m/z = 429.1 (M-Boc).

[00986] Step C: Preparation of (R)-tert-butyl 2-(((4-chloro-5-(3-((2'R,3'R)-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)ureido)-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate: To a solution of (2'R,3'R)-3'-amino-2',3'-

dihydrospiro[cyclopropane-1,1'-inden]-2'-ol (Intermediate X9, 24.2 mg, 0.138 mmol) in iPrOH (1.4 mL) was added (R)-*tert*-butyl 2-(((4-chloro-5-((phenoxycarbonyl)amino)-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate (73 mg, 0.138 mmol). The reaction mixture was stirred at ambient temperature for 16 hours, then was diluted with DCM (2 mL) and purified by silica column chromatography, eluting with 0-10% MeOH/DCM, to afford the product as an off-white solid (64 mg, 76% yield). MS (apci) m/z = 510.2 (M-Boc).

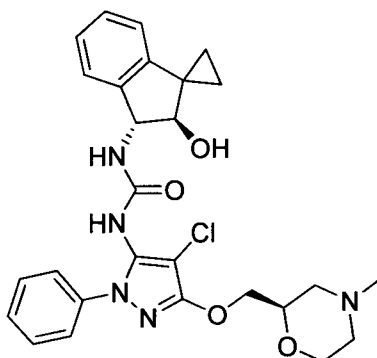
Example 140



1-(4-chloro-3-(((R)-morpholin-2-ylmethoxy))-1-phenyl-1H-pyrazol-5-yl)-3-((2'R,3'R)-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)urea

[00987] To a suspension of (R)-*tert*-butyl 2-(((4-chloro-5-(3-((2'R,3'R)-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)ureido)-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate (Example 139, 61 mg, 0.100 mmol) in iPrOH (0.2 mL) was added HCl (5-6M in iPrOH, 500 μ L). The reaction mixture was stirred at ambient temperature for 19 hours, then was diluted with saturated aqueous NaHCO₃ (10 mL) and extracted with DCM (15 mL). The aqueous phase was diluted with H₂O (5 mL), then the aqueous phase was extracted with 10% MeOH/90% DCM (2 x 10 mL). The combined organic phases were dried (MgSO₄), filtered, concentrated, and dried under high vacuum to give the product as a white solid (44.7 mg, 88% yield). MS (apci) m/z = 510.2 (M+H).

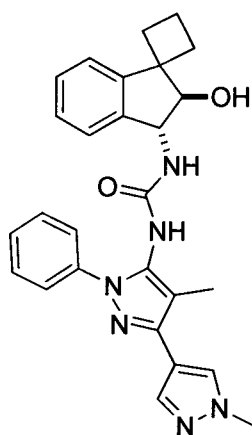
Example 141



1-(4-chloro-3-(((R)-4-methylmorpholin-2-ylmethoxy))-1-phenyl-1H-pyrazol-5-yl)-3-((2'R,3'R)-

2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)urea

[00988] To a suspension of 1-(4-chloro-3-((R)-morpholin-2-ylmethoxy)-1-phenyl-1H-pyrazol-5-yl)-3-((2'R,3'R)-2'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-3'-yl)urea (Example 140, 25 mg, 0.049 mmol) in DCE (1 mL) were added paraformaldehyde (3.5 mg, 0.117 mmol) then sodium triacetoxyborohydride (15.6 mg, 0.074 mmol). The reaction mixture was stirred at ambient temperature for 16 hours, then at 50 °C for 1 hour. Additional sodium triacetoxyborohydride (8 mg, 0.038 mmol) was added and the reaction mixture was stirred at ambient temperature for 1 hour, then additional sodium triacetoxyborohydride (8 mg, 0.038 mmol) was added and the reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was diluted with DCM (10 mL) and saturated aqueous NaHCO₃ (10 mL). The phases were separated and the aqueous phase was extracted with 10% MeOH/90% DCM (2 x 10 mL). The combined organic phases were dried (MgSO₄), filtered, and concentrated. The crude product was purified by silica column chromatography, eluting with 0-10% NH₃/MeOH in DCM, to afford the product as a white solid (14.3 mg, 56% yield). MS (apci) m/z = 524.2 (M+H).

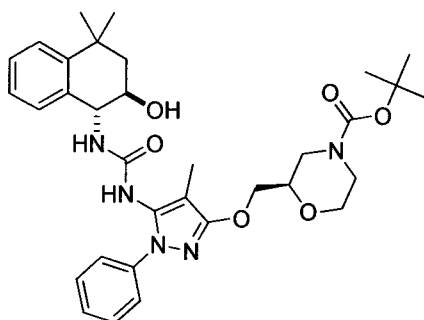
Example 142

1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(trans-2'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-inden]-3'-yl)urea

[00989] Step A: Preparation of spiro[cyclobutane-1,1'-indene]: To a solution of 1H-indene (1.00 g, 8.609 mmol) and 1,3-dibromopropane (967 μ L, 9.470 mmol) in DMSO (43 mL) was added KOtBu (2.125 g, 18.939 mmol) in 4 portions over 5 min. The reaction mixture was stirred at ambient temperature for 3 days, then was diluted with H₂O (50 mL) and extracted with Et₂O (3 x 50 mL). The combined organic phases were washed with H₂O (50 mL), then brine (3 x 50 mL), then dried (MgSO₄), filtered, and concentrated. The crude oil was purified by silica column chromatography, eluting with hexanes, to afford the product as a colorless oil (0.57 g, 42% yield).

[00990] Step B: Preparation of 1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(*trans*-2'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-inden]-3'-yl)urea: Prepared according to the procedure of Example 55, Steps B-D, replacing spiro[cyclopropane-1,1'-indene] in Step B with spiro[cyclobutane-1,1'-indene]. The reaction mixture was purified by silica column chromatography, eluting with 0-60% acetone/hexanes, to afford the product as a white solid (5.2 mg, 42% yield). MS (apci) $m/z = 469.2$ (M+H).

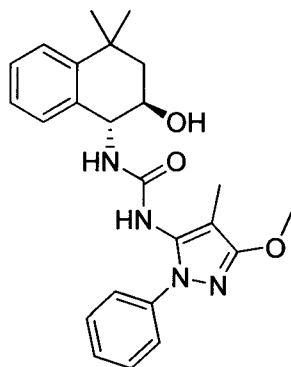
Example 143



(R)-tert-butyl 2-(((5-(3-(*trans*-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ureido)-4-methyl-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate

[00991] Step A: Preparation of (R)-tert-butyl 2-(((4-methyl-5-((phenoxycarbonyl)amino)-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate: To a solution of (R)-tert-butyl 2-(((5-amino-4-methyl-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate (Intermediate Y7, 20 mg, 0.0515 mmol) in EtOAc (0.5 mL) were added aqueous NaOH (2M, 51 μ L, 0.103 mmol) then phenyl chloroformate (10 μ L, 0.077 mmol). The reaction mixture was stirred at ambient temperature for 4 days, then transferred to separatory funnel with EtOAc (10 mL). The phases were separated and the organic phase was washed with H₂O (10 mL), brine (10 mL), dried (MgSO₄), filtered, and concentrated to a thick syrup. Added hexanes (10 mL), sonicated, decanted hexanes, then dried under high vacuum to afford the product as an orange solid (20.5 mg, 78% yield). MS (apci) $m/z = 509.2$ (M+H).

[00992] Step B: Preparation of (R)-tert-butyl 2-(((5-(3-(*trans*-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ureido)-4-methyl-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate: To a solution of (R)-tert-butyl 2-(((4-methyl-5-((phenoxycarbonyl)amino)-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate (20 mg, 0.033 mmol) in iPrOH (0.5 mL) was added *trans*-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Intermediate X1, 7.5 mg, 0.039 mmol). The reaction mixture was stirred at ambient temperature for 18 hours, then directly purified by silica column chromatography, eluting with 0-10% MeOH/DCM, to afford the product as an off-white solid (13.7 mg, 53% yield). MS (apci) $m/z = 606.3$ (M+H).

Example 144

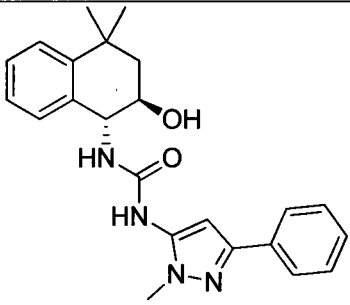
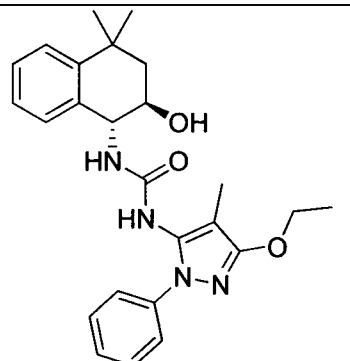
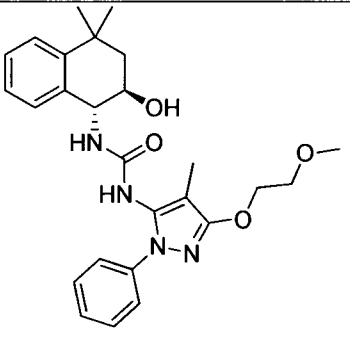
1-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea

[00993] Step A: Preparation of phenyl (3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)carbamate: To a solution of 3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-amine (Intermediate 2, 646 mg, 3.179 mmol) in EtOAc (32 mL) were added aqueous NaOH (2M, 3.18 mL, 6.357 mmol) then phenyl chloroformate (0.5981 mL, 4.768 mmol). The reaction mixture was stirred at ambient temperature for 17 hours and then transferred to separatory funnel with EtOAc (25 mL). The phases were separated and the organic phase was washed with H₂O (25 mL), brine (25 mL), dried (MgSO₄), filtered, and concentrated to a thick syrup. Hexane (10 mL) was added, and the mixture was sonicated. The hexanes were decanted and then dried under high vacuum to afford the product as a pale yellow solid (908 mg, 88% yield). MS (apci) m/z = 324.1 (M+H).

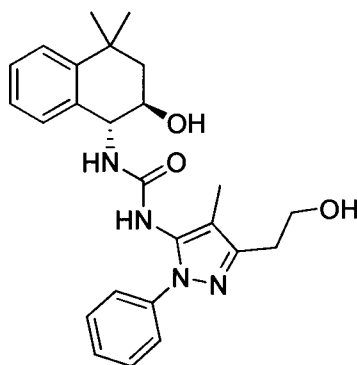
[00994] Step B: Preparation of 1-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea: To (1R,2R)-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Intermediate X2, 198 mg, 1.04 mmol) were added iPrOH (5 mL) and phenyl (3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)carbamate (335 mg, 1.04 mmol). The reaction mixture was heated to 70 °C for 45 minutes, then cooled to ambient temperature. The suspension was filtered, rinsed with iPrOH (2 x 0.5 mL) then Et₂O (5 x 1 mL). The solid was collected, then recrystallized in iPrOH (2 mL), to afford the product as a white solid (95 mg, 22% yield). MS (apci) m/z = 421.2 (M+H).

[00995] The examples in Table 5 were prepared according to the procedure of Example 144, substituting the appropriate aminopyrazole intermediate in Step A.

Table 5

Ex. #	Structure	Name	MS (apci) m/z
145		1-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(1-methyl-3-phenyl-1H-pyrazol-5-yl)urea	391.2 (M+H)
146		1-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)urea	435.3 (M+H)
147		1-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(2-methoxyethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea	465.3 (M+H)

Example 148



1-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(2-hydroxyethyl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea

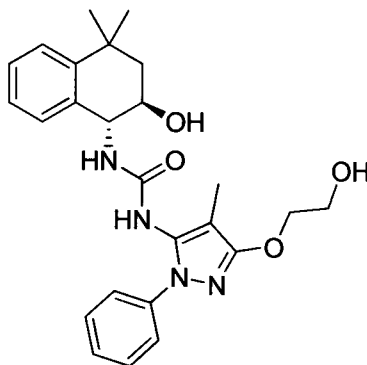
[00996]

Step A: Preparation of 1-(3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-methyl-1-

phenyl-1H-pyrazol-5-yl)-3-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)urea: Prepared according to the procedure of Example 144, replacing 3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-amine in Step A with 3-(2-(tert-butyldimethylsilyloxy)ethyl)-4-methyl-1-phenyl-1H-pyrazol-5-amine (Intermediate Y9). The reaction mixture was purified by silica column chromatography, eluting with 0-60% acetone/hexanes, to afford the product as a pale yellow solid (26.8 mg, 47% yield). MS (apci) m/z = 549.3 (M+H).

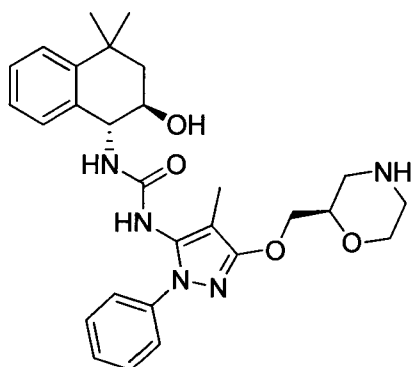
[00997] Step B: Preparation of 1-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(2-hydroxyethyl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea: To a solution of 1-(3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)urea (26.8 mg, 0.0488 mmol) in EtOH (0.5 mL) was added HCl (5-6M in iPrOH, 0.2 mL). The reaction mixture was stirred at ambient temperature for 2 hours. The reaction mixture was concentrated, then diluted with Et₂O (3 x 3 mL) and concentrated after each addition, and dried under high vacuum to afford the product as a pale yellow solid (24.1 mg, 113% yield). MS (apci) m/z = 435.3 (M+H).

Example 149



1-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(2-hydroxyethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea

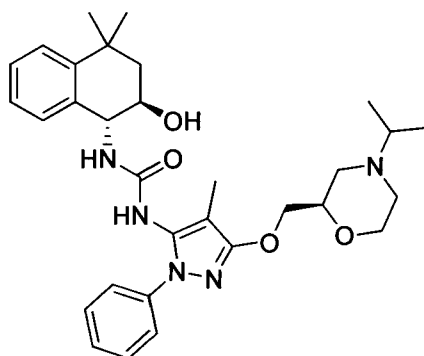
[00998] Prepared according to the procedure of Example 148, replacing 3-(2-(tert-butyldimethylsilyloxy)ethyl)-4-methyl-1-phenyl-1H-pyrazol-5-amine in Step A with 3-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-amine (Intermediate P203), to afford the product as an off-white solid (33.7 mg, 106% yield). MS (apci) m/z = 451.3 (M+H).

Example 150

1-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-((R)-morpholin-2-ylmethoxy)-1-phenyl-1H-pyrazol-5-yl)urea

[00999] Step A: Preparation of (R)-tert-butyl 2-(((5-(3-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ureido)-4-methyl-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate: Prepared according to the procedure of Example 143, replacing *trans*-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol in Step B with (1R,2R)-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (Intermediate X2), to afford the product as a pale yellow solid (134 mg, 75% yield). MS (apci) m/z = 606.3 (M+H).

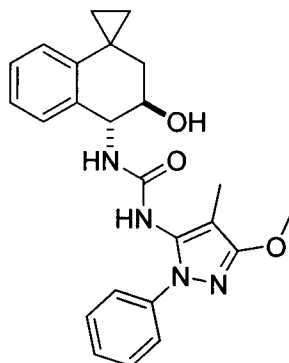
[001000] Step B: Preparation of 1-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-((R)-morpholin-2-ylmethoxy)-1-phenyl-1H-pyrazol-5-yl)urea: To a solution of (R)-tert-butyl 2-(((5-(3-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ureido)-4-methyl-1-phenyl-1H-pyrazol-3-yl)oxy)methyl)morpholine-4-carboxylate (134 mg, 0.221 mmol) in iPrOH (3 mL) was added HCl (5-6M in iPrOH, 350 μ L). The reaction mixture was stirred at ambient temperature for 17 hours, then additional HCl (5-6M in iPrOH, 1 mL) was added. The reaction mixture was stirred at ambient temperature for 24 hours, then diluted with saturated aqueous NaHCO₃ (25 mL) and extracted with DCM (3 x 25 mL). The combined organic phases were dried (MgSO₄), filtered, concentrated, and dried under high vacuum to give the product as a yellowish-tan solid (99 mg, 81% yield). MS (apci) m/z = 506.3 (M+H).

Example 151

1-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-(((R)-4-isopropylmorpholin-2-yl)methoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea

[001001] To a suspension of 1-((1R,2R)-2-hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-((R)-morpholin-2-ylmethoxy)-1-phenyl-1H-pyrazol-5-yl)urea (Example 150, 20 mg, 0.040 mmol) in DCE (0.5 mL) were added acetone (29 μ L, 0.396 mmol) then NaBH(OAc)₃ (13 mg, 0.059 mmol). The reaction mixture was stirred at ambient temperature for 19 hours, then additional acetone (60 μ L, 0.817 mmol) and NaBH(OAc)₃ (20 mg, 0.094 mmol). The reaction mixture was stirred at ambient temperature for 2 hours, then diluted with DCM (10 mL) and saturated aqueous NaHCO₃ (10 mL). The phases were separated and the aqueous phase was extracted with 10% MeOH/90% DCM (2 x 10 mL). The combined organic phases were dried (MgSO₄), filtered, and concentrated. The crude product was purified by silica column chromatography, eluting with 0-10% NH₃/MeOH in DCM, to afford the product as a white solid (16.3 mg, 75% yield). MS (apci) m/z = 548.3 (M+H).

Example 152

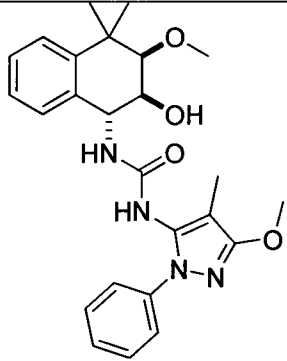
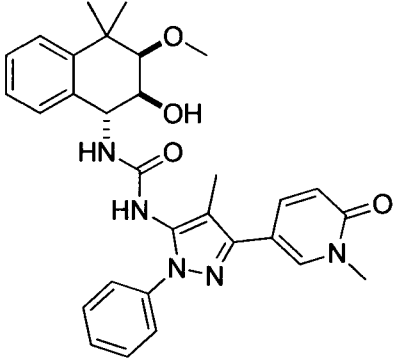
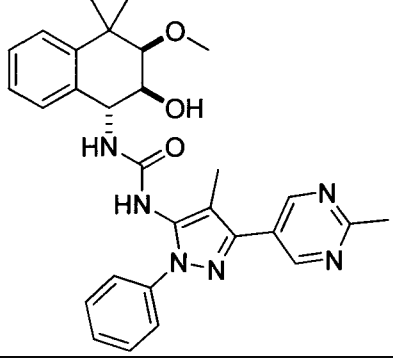


1-((trans-3'-hydroxy-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-4'-yl)-3-(3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea

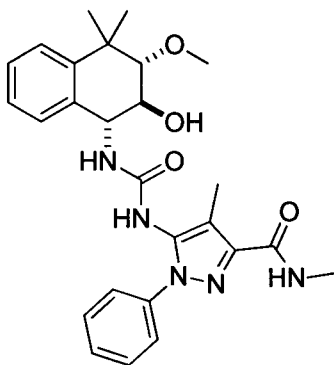
[001002] Prepared according to the procedure of Example 144, replacing (1R,2R)-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol in Step B with *trans*-4'-amino-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3'-ol (Intermediate X11). The reaction mixture was purified by silica column chromatography, eluting with 0-10% NH₃/MeOH in DCM, to afford the product as a white solid (5.0 mg, 40% yield). MS (apci) m/z = 419.2 (M+H).

[001003] The following examples in Table 6 were prepared according to the procedure of Example 85, using the appropriate aminopyrazole intermediate.

Table 6

Ex. #	Structure	Name	MS (apci) m/z
153		1-((<i>r</i> -1, <i>t</i> -2, <i>t</i> -3)-2-hydroxy-3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea	451.2 (M+H)
154		1-((<i>r</i> -1, <i>t</i> -2, <i>t</i> -3)-2-hydroxy-3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)urea	528.2 (M+H)
155		1-((<i>r</i> -1, <i>t</i> -2, <i>t</i> -3)-2-hydroxy-3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-yl)urea	513.2 (M+H)

Example 156



5-(3-((*r*-1,*t*-2,*c*-3)-2-hydroxy-3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ureido)-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide

[001004] Step A: Preparation of (*r*-1a,*c*-2,*t*-7b)-3,3-dimethyl-1a,2,3,7b-

tetrahydronaphtho[1,2-b]oxiren-2-ol: Stirred 1,1-dimethyl-1,2-dihydronaphthalen-2-ol (Example 85, Step C, 1.2 g, 6.89 mmol) with 1,2-dichloroethane (15 mL) in an ice bath and added saturated aqueous NaHCO₃ (15 mL). 3-chlorobenzoperoxoic acid (2.55 g, 10.3 mmol) was added and the reaction mixture was allowed to warm to ambient temperature and stir overnight. The mixture was diluted with water (30 mL) and DCM (30 mL). The phases were separated and the aqueous phase was extracted with DCM (30 mL). The combined organic layers were washed with 2N NaOH (30 mL), dried (MgSO₄), filtered, and concentrated. The crude product was purified by silica gel column chromatography, eluting with 25% EtOAc/hexanes followed by 40% EtOAc/hexanes. Yield: 662 mg (51%).

[001005] Step B: Preparation of (*r*-1a,*c*-2,*t*-7b)-2-methoxy-3,3-dimethyl-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene: A round bottomed flask was charged with (*r*-1a,*c*-2,*t*-7b)-3,3-dimethyl-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxiren-2-ol (662 mg, 3.48 mmol) and anhydrous DMF (10 mL). The reaction mixture was chilled in an ice bath and sodium hydride (209 mg, 5.22 mmol; 60% in oil) was added in portions over 10 minutes under a stream of N₂. The reaction mixture was stirred for 30 minutes in ice bath, and then iodomethane (433 µL, 6.96 mmol) was added. The flask was removed from ice bath and the reaction mixture was warmed to ambient temperature and stirred for 30 minutes. The reaction mixture was carefully quenched with saturated aqueous NH₄Cl (10 mL), then diluted with H₂O (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with water (20 mL), brine (20 mL), dried (MgSO₄), filtered, and concentrated. The crude material was used in the next step without further purification (assuming theoretical yield). Yield: 777 g (109%).

[001006] Step C: Preparation of (*r*-1,*t*-2,*c*-3)-1-amino-3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol: The title compound was prepared from (*r*-1a,*c*-2,*t*-7b)-2-methoxy-3,3-dimethyl-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene (711 mg, 3.48 mmol) according to the procedure described for Example 79, Step E. Yield: 315 mg (41%).

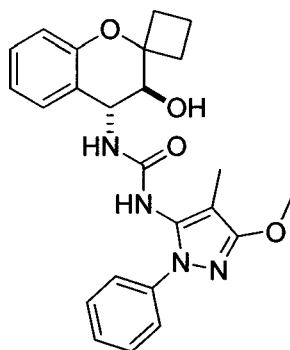
[001007] Step D: Preparation of 5-(3-((*r*-1,*t*-2,*c*-3)-2-hydroxy-3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ureido)-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide: The title compound was prepared from (*r*-1,*t*-2,*c*-3)-1-amino-3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (20 mg, 0.090 mmol) and 5-amino-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide (Intermediate 10; 21 mg, 0.090 mmol) according to the procedure described for Example 79, Step F. Yield: 4 mg (9%). MS *m/z* (APCI-pos) *M*+1 = 478.2.

[001008] The compounds in Table 7 were prepared according to the procedure of Example 156, using the appropriate aminopyrazole intermediate.

Table 7

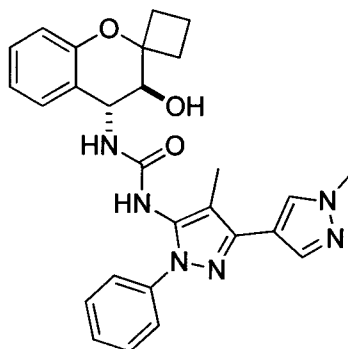
Ex. #	Structure	Name	MS (apci) m/z
157		1-((1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-((r-1,t-2,c-3)-2-hydroxy-3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)urea	501.2 (M+H)
158		1-((r-1,t-2,c-3)-2-hydroxy-3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-(4-methyl-3-((1-methylpiperidin-4-yl)methoxy)-1-phenyl-1H-pyrazol-5-yl)urea	548.3 (M+H)

Example 159



1-((trans-3-hydroxyspiro[chroman-2,1'-cyclobutan]-4-yl)-3-(3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea

[001009] Prepared according to the procedure of Example 144, replacing (1R,2R)-1-amino-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol in Step B with *trans*-4-aminospiro[chroman-2,1'-cyclobutan]-3-ol (Intermediate X12, 10 mg, 0.049 mmol). The reaction mixture was purified by silica column chromatography, eluting with 0-50% acetone/hexanes, to afford the product as a white solid (17.2 mg, 81% yield). MS (apci) m/z = 435.3 (M+H).

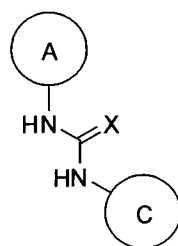
Example 160

1-(1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)-3-(trans-3-hydroxyspiro[chroman-2,1'-cyclobutan]-4-yl)urea

[001010] Prepared according to the procedure of Example 159, replacing phenyl (3-methoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)carbamate with phenyl (1',4-dimethyl-1-phenyl-1H,1'H-[3,4'-bipyrazol]-5-yl)carbamate (Intermediate 13, 18.2 mg, 0.049 mmol). The reaction mixture was filtered and rinsed Et₂O (3 x 0.5 mL) to afford the product as a white solid (17.1 mg, 72% yield). MS (apci) m/z = 485.2 (M+H).

What is claimed is:

1. A compound having the Formula **I-2**:

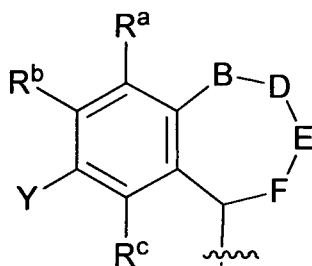


I

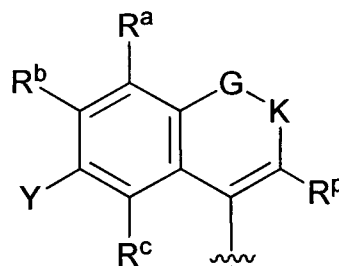
or stereoisomers, tautomers, or pharmaceutically acceptable salts, or solvates thereof, wherein:

X is O, S, NH or N-CN;

Ring A is formula A-1 or A-2



A-1



A-2

Y is H, halogen, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkyl [optionally substituted with 1-5 fluoros], cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, aminocarbonyl(1-6C)alkyl, (1-6C)alkoxy [optionally substituted with 1-5 fluoros], CN, aminocarbonyl or (1-4C alkoxy)carbonyl;

R^a, R^b and R^c are independently selected from H, halogen, (1-3C)alkyl, (1-3C)alkoxy and CN;

B is NR¹, O, a bond, CR^dR^e, S or SO₂;

D is NR¹, O, a bond, CR^fR^g, S or SO₂;

E is NR¹, O, a bond, or CR^hRⁱ, S or SO₂;

F is CR^jR^k;

provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms and zero or one of B, D or E is NR¹ or O;

G is CR^mRⁿ;

K is NR¹;

R^1 is (1-6C)alkyl [optionally substituted with one to five fluoros], (1-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], (1-6C)alkylC(=O)- or (1-6C alkoxy)C=O-;

R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently H, OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], (2-6C)cyanoalkyl, (1-6C)alkoxy [optionally substituted with one to five fluoros], or (1-3C alkoxy)(2-6C)alkoxy [optionally substituted with one to five fluoros],

or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring,

or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k form an oxo group,

and wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom;

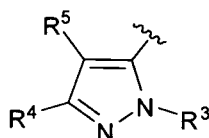
R^m is H, (1-3C)alkyl [optionally substituted with 1-5 fluoros], cyclopropyl or cyclobutyl, and

R^n is H or (1-3C)alkyl [optionally substituted with 1-5 fluoros], or

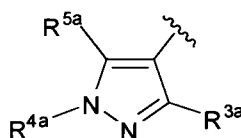
R^m and R^n together form an oxo group;

R^p is H, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], or (2-6C)cyanoalkyl;

Ring C is formula **C-1** or **C-2**



C-1



C-2

;

R^3 is (1-6C)alkyl, hydroxy(1-6C)alkyl, Ar^2 , hetCyc¹, (3-7C)cycloalkyl, or hetAr²;

Ar^2 is phenyl optionally substituted with one or more groups independently selected from halogen and (1-6C)alkyl;

hetCyc¹ is a 5-6-membered saturated or partially unsaturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

hetAr² is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

R⁴ is OH, (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, (1-3C)alkylsulfonamido(1-6C)alkyl, sulfamido(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, hetAr³(1-6C)alkyl, Ar³(1-6C)alkyl, (1-6C)alkoxy, monofluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, tetrafluoro(2-6C)alkoxy, pentafluoro(2-6C)alkoxy, cyano(1-6C)alkoxy, hydroxy(1-6C)alkoxy, dihydroxy(2-6C)alkoxy, amino(2-6C)alkoxy, hydroxylcarbonyl(1-6C)alkoxy, hetCyc²(1-6C)alkoxy, hetAr³(1-6C)alkoxy, Ar³(1-6C)alkoxy, (1-4C alkoxy)(1-6C)alkoxy, (1-3C alkylsulfonyl)(1-6C)alkoxy, (3-6C)cycloalkyl [optionally substituted with F, OH, (1-6C alkyl), (1-6C) alkoxy, or (1-3C alkoxy)(1-6C)alkyl], hetAr⁴, hetAr⁴-O-, Ar⁴, hetCyc²(O)CH₂-, (1-4C alkoxycarbonyl)(1-6C)alkoxy, hydroxycarbonyl(1-6C)alkoxy, aminocarbonyl(1-6C)alkoxy, hetCyc²C(=O)(1-6C)alkoxy, hydroxy(1-3C alkoxy)(1-6C)alkoxy, hydroxytrifluoro(1-6C)alkoxy, (1-3C)alkylsulfonamido(1-6C)alkoxy, (1-3C)alkylamido(1-6C)alkoxy, di(1-3C alkyl)amino-carboxy, hetCyc²C(=O)O-, hydroxydifluoro(1-6C)alkyl, (1-4C alkylcarboxy)(1-6C)alkyl, (1-6C)alkoxycarbonyl, hydroxylcarbonyl, aminocarbonyl, (1-3C alkoxy)aminocarbonyl, hetCyc³, halogen, CN, trifluoromethylsulfonyl, N-(1-3C alkyl)oxadiazolonyl, hetAr⁵ or hetCyc⁴-O-;

hetCyc² is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with 1-2 groups independently selected from (1-6C)alkyl, (1-4C alkylcarboxy)(1-6C)alkyl, and (1-6C)acyl;

hetCyc³ is a 4-7 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from F, CN, (1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-6C)acyl-, (1-6C)alkylsulfonyl, trifluoromethylsulfonyl and (1-4C alkoxy)carbonyl;

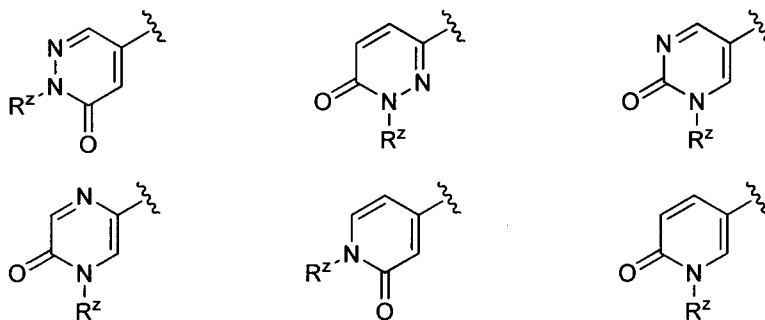
hetAr³ is a 5-membered heteroaryl ring having 1-3 ring atoms independently selected from N, O and S and optionally substituted with (1-6C)alkyl;

Ar³ is phenyl optionally substituted with (1-4C)alkoxy;

hetAr⁴ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with one or more substituents independently

selected from (1-6C)alkyl, halogen, CN, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, difluoro(1-6C)alkyl, fluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH₂-, (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH₂, (1-6C alkyl)amino, di(1-6C alkyl)amino, (1-3C trifluoroalkoxy), fluoro(1-6C alkyl)amino, difluoro(1-6C alkyl)amino, trifluoro(1-6C alkyl)amino, and (3-4C cycloalkyl)amino;

hetAr⁵ is a group selected from the structures:



where R^z is (3-4C)cycloalkyl or (1-3C)alkyl (optionally substituted with 1-3 fluoros), wherein each of said hetAr⁵ groups is optionally further substituted with one or more groups independently selected from F and (1-3C)alkyl optionally substituted with 1-3 fluoros;

hetCyc⁴ is a 7-8 membered bridged heterocycle having a ring nitrogen atom and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

Ar⁴ is phenyl optionally substituted with one or more groups independently selected from (1-6C)alkyl, halogen, CN, CF₃, CF₃O-, (1-6C)alkoxy, (1-6Calkyl)OC(=O)-, aminocarbonyl, (1-6C)alkylthio, hydroxy(1-6C)alkyl, (1-6C alkyl)SO₂-, HOC(=O)- and (1-3C alkoxy)(1-3C alkyl)OC(=O)-;

R⁵ is (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-3C alkoxy)(1-4C)alkyl, (1-4C alkyl)OC(=O)-, (1-6C)alkylthio, (3-4C)cycloalkyl, amino, aminocarbonyl, trifluoro(1-3C alkyl)amido, or phenyl (optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl and (1-6C)alkoxy); or

R⁴ and R⁵ together with the atoms to which they are attached form a 5-6 membered saturated, partially unsaturated or unsaturated carbocyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl, or

R⁴ and R⁵ together with the atoms to which they are attached form 5-6 membered saturated, partially unsaturated or unsaturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or two

substituents independently selected from (1-6C alkyl)C(=O)O-, (1-6C)acyl, (1-6C)alkyl and oxo, and said sulfur ring atom is optionally oxidized to S(=O) or SO₂;

R^{3a} is halogen, (1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (1-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

R^{4a} is hydrogen, (1-6C)alkyl, trifluoro(1-6C)alkyl, phenyl [optionally substituted with one or more groups independently selected from (1-6C)alkyl, halogen, CN, CF₃, CF₃O-, (1-6C)alkoxy, (1-6C)alkyl)OC(=O)-, aminocarbonyl, (1-6C)alkylthio, hydroxy(1-6C)alkyl, (1-6C)alkyl)SO₂-, HOC(=O)- and (1-3C alkoxy)(1-3C alkyl)OC(=O)-], or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with 1-2 substituents independently selected from (1-6C)alkyl, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH₂-, (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH₂, (1-6C alkyl)amino, di(1-6C alkyl)amino and (1-3C trifluoroalkoxy)(1-3C)trifluoroalkyl; and

R^{5a} is halogen, (1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (1-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen.

2. A compound according to claim 1, wherein X is O.
3. A compound according to claim 1, wherein X is S.
4. A compound according to any of claims 1-3, wherein zero to four of R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j and R^k are independently H, OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], (2-6C)cyanoalkyl, (1-6C)alkoxy [optionally substituted with one to five fluoros], or (1-3C alkoxy)(2-6C)alkoxy [optionally substituted with one to five fluoros],

or one of a pair of R^d and R^e, or R^f and R^g, or R^h and Rⁱ, or R^j and R^k, together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring, or one of a pair of R^d and R^e, or R^f and R^g, or R^h and Rⁱ, or R^j and R^k form an oxo group, and the remainder are hydrogen, wherein only one of R^d and R^e can be OH and neither is OH if B is

connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom.

5. A compound according to claim 4, wherein zero to two of R^d , R^e , R^f , R^g , R^h , R^i , R^j and R^k are independently OH, methyl, methoxy, $\text{CH}_3\text{OCH}_2\text{CH}_2\text{O}-$, or cyclopropyl,

or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k , together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidiny ring, or one of a pair of R^d and R^e , or R^f and R^g , or R^h and R^i , or R^j and R^k form an oxo group, and the remainder are hydrogen, wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom.

6. A compound according to any of claims 1-5, wherein Ring A is A-1.

7. A compound according to claim 6, wherein B is a bond or CR^dR^e , D is a bond or CR^fR^g , E is a bond or CR^hR^i , and F is CR^jR^k , provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms.

8. A compound according to claim 6, wherein B is O, a bond or CR^dR^e , D is O, a bond or CR^fR^g , E is O, a bond or CR^hR^i , and F is CR^jR^k , provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms and contains one oxygen atom.

9. A compound according to claim 6, wherein B is NR^1 , a bond or CR^dR^e , D is NR^1 , a bond or CR^fR^g , E is NR^1 , a bond or CR^hR^i , and F is CR^jR^k , provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms and contains one nitrogen atom.

10. A compound according to claim 6, wherein B is a NR^1 or O, D is a bond or CR^fR^g , E is a bond or CR^hR^i , and F is CR^jR^k , provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms.

11. A compound according to claim 6, wherein B is a bond or CR^dR^e , D is NR^1 or O, E is a bond or CR^hR^i , and F is CR^jR^k , provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms.

12. A compound according to any of claims 1-5, wherein Ring A is A-2.

13. A compound according to any of claims 1-12, wherein Y is H, halogen or (1-3C alkoxy)(1-6C)alkyl.

14. A compound according to any of claims 1-13, wherein R^a, R^b and R^c are independently selected from halogen, (1-3C)alkyl, (1-3C)alkoxy and CN.

15. A compound according to any of claims 1-14, wherein Ring C is formula C-1.

16. A compound according to claim 15, wherein:

R⁴ is OH, (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, (1-3C)alkylsulfonamido(1-6C)alkyl, sulfamido(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, hetAr³(1-6C)alkyl, Ar³(1-6C)alkyl, (1-6C)alkoxy, monofluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, tetrafluoro(2-6C)alkoxy, pentafluoro(2-6C)alkoxy, cyano(1-6C)alkoxy, hydroxy(1-6C)alkoxy, dihydroxy(2-6C)alkoxy, amino(2-6C)alkoxy, hydroxylcarbonyl(1-6C)alkoxy, hetCyc²(1-6C)alkoxy, hetAr³(1-6C)alkoxy, Ar³(1-6C)alkoxy, (1-4C alkoxy)(1-6C)alkoxy, (1-3C alkylsulfonyl)(1-6C)alkoxy, (3-6C)cycloalkyl [optionally substituted with F, OH, (1-6C alkyl), (1-6C) alkoxy, or (1-3C alkoxy)(1-6C)alkyl], hetAr⁴, hetAr⁴-O-, Ar⁴, hetCyc²(O)CH₂-, (1-4C alkoxycarbonyl)(1-6C)alkoxy, hydroxycarbonyl(1-6C)alkoxy, aminocarbonyl(1-6C)alkoxy, hetCyc²C(=O)(1-6C)alkoxy, hydroxy(1-3C alkoxy)(1-6C)alkoxy, hydroxytrifluoro(1-6C)alkoxy, (1-3C)alkylsulfonamido(1-6C)alkoxy, (1-3C)alkylamido(1-6C)alkoxy, di(1-3C alkyl)amino-carboxy, hetCyc²C(=O)O-, hydroxydifluoro(1-6C)alkyl, (1-4C alkylcarboxy)(1-6C)alkyl, (1-6C)alkoxycarbonyl, hydroxylcarbonyl, aminocarbonyl, (1-3C alkoxy)aminocarbonyl, hetCyc³, halogen, CN, trifluoromethylsulfonyl, N-(1-3C alkyl)oxadiazolonyl, or hetAr⁵;

and

R⁵ is (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-3C alkoxy)(1-4C)alkyl, (1-4C alkyl)OC(=O)-, (1-6C)alkylthio, (3-4C)cycloalkyl, amino, aminocarbonyl, trifluoro(1-3C alkyl)amido, or phenyl (optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl and (1-6C)alkoxy).

17. A compound according to claim 16, wherein R⁴ is selected from (1-6C)alkyl, trifluoro(1-6C)alkyl, cyano(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, cyano(1-6C)alkoxy, hydroxy(1-6C)alkoxy, (1-4C alkoxy)(1-6C)alkoxy, (3-6C)cycloalkyl, hetAr⁴ and hetAr⁵.

18. A compound according to claim 16, wherein R⁴ is selected from (1-6C)alkoxy, hetAr⁴ and hetAr⁵.

19. A compound according to claim 17, wherein R⁴ is hetAr⁴ or hetAr⁵.

20. A compound according to any of claims 1-19, wherein R⁵ is selected from halogen, CN, (1-6C)alkyl, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-6C)alkylthio, or phenyl optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl and (1-6C)alkoxy.

21. A compound according to claim 20, wherein R⁵ is selected from halogen and (1-6C)alkyl.

22. A compound according to claim 21, wherein R⁵ is (1-6C)alkyl.

23. A compound according to claim 15, wherein:

R⁴ and R⁵ together with the atoms to which they are attached form a 5-6 membered saturated carbocyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl, or

R⁴ and R⁵ together with the atoms to which they are attached form a 5-6 membered saturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said ring nitrogen atom is optionally substituted with (1-6C alkyl)C(=O)O-, or (1-6)acyl, and said sulfur ring atom is optionally oxidized to S(=O) or SO₂.

24. A compound according to any of claims 1-23, wherein R³ is selected from Ar², hetAr² and (1-6C)alkyl.

25. A compound according to any of claims 1-24, wherein R³ is selected from Ar² and (1-6C)alkyl.

26. A compound according to claim 25, wherein R³ is Ar².

27. A compound according to claim 1, selected from a compound of Examples 1-160 or a pharmaceutically acceptable salt thereof.

28. A pharmaceutical composition, which comprises a compound of Formula I as defined in any one of claims 1 to 27 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

29. A method for treating a disease or disorder selected from pain, cancer, inflammation/inflammatory diseases, neurodegenerative diseases, certain infectious diseases, Sjogren's syndrome, endometriosis, diabetic peripheral neuropathy, prostatitis and pelvic pain syndrome in a mammal, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I as defined in any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof.

30. The method of claim 29, wherein the method is a method of treating pain.

31. The method of claim 29, wherein said cancer is a cancer having a dysregulation of TrkA.

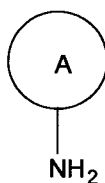
32. The method of claim 31, wherein said cancer is selected from non-small cell lung cancer, papillary thyroid carcinoma, glioblastoma multiforme, acute myeloid leukemia, colorectal carcinoma, large cell neuroendocrine carcinoma, prostate cancer, neuroblastoma, pancreatic carcinoma, melanoma, head and neck squamous cell carcinoma and gastric carcinoma.

33. A compound of Formula I as defined in any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, for use in the treatment of pain, cancer, inflammation/inflammatory diseases, neurodegenerative diseases, certain infectious diseases, Sjogren's syndrome, endometriosis, diabetic peripheral neuropathy, prostatitis and pelvic pain syndrome.

34. Use of a compound of Formula I as defined in any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating pain, cancer, inflammation/inflammatory diseases, neurodegenerative diseases, certain infectious diseases, Sjogren's syndrome, endometriosis, diabetic peripheral neuropathy, prostatitis and pelvic pain syndrome.

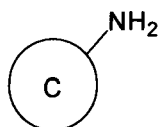
35. A process for the preparation of a compound of claim 1, which comprises:

(a) for a compound of Formula I where X is O, coupling a corresponding compound having the formula II



II

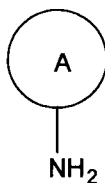
with a corresponding compound having the formula III



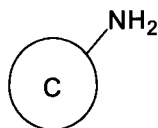
III

in the presence carbonyldiimidazole or triphosgene and a base; or

(b) for a compound of Formula I where X is S, coupling a corresponding compound having the formula II

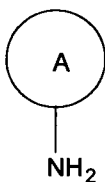
**II**

with a corresponding compound having the formula **III**

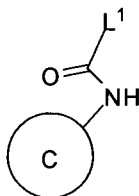
**III**

in the presence di(1H-imidazol-2-yl)methanethione and a base; or

(c) for a compound of Formula **I** where X is O, coupling a corresponding compound having the formula **II**

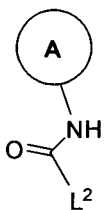
**II**

with a corresponding compound having the formula **IV**

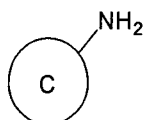
**IV**

where L¹ is a leaving group, in the presence of a base; or

(d) for a compound of Formula **I** where X is O, coupling a corresponding compound having the formula **V**

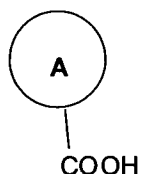
**V**

where L² is a leaving group, with a corresponding compound having the formula **III**

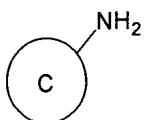
**III**

in the presence of a base; or

(e) for a compound of Formula I where X is O, activating a corresponding compound having the formula VI

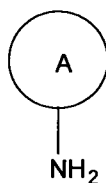
**VI**

with diphenylphosphoryl azide followed by coupling the activated intermediate with a corresponding compound having the formula III

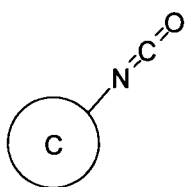
**III**

in the presence a base; or

(f) for a compound of Formula I where X is O, coupling a corresponding compound having the formula II

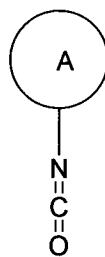
**II**

with a corresponding compound having the formula VII

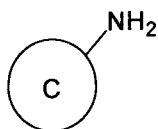
**VII**

in the presence of a base; or

(g) for a compound of Formula I where X is O, coupling a corresponding compound having the formula VIII

**VIII**

with a corresponding compound having the formula **III**

**III**

in the presence of a base; and

optionally removing protecting groups and optionally preparing a pharmaceutically acceptable salt thereof.